In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: August 29, 2023

WILBERT L. TOWNSEND, SR.,	*	PUBLISHED
Petitioner,	*	No. 14-266V
v.	*	Special Master Nora Beth Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Dismissal; Influenza ("Flu") Vaccine; Multiple Sclerosis ("MS").
Respondent.	*	

James E. McCollum, Jr., McCollum & Associates, LLC, College Park, Maryland, for Petitioner.
Ryan Daniel Pyles, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION[1]

I. INTRODUCTION

On April 7, 2014, Wilbert L. Townsend, Sr. ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10 et seq. (2018).[2] Petitioner alleged that he suffered multiple

[1] Because this Decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2018) ("Vaccine Act" or "the Act"). All citations in this Decision to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

sclerosis ("MS")[3] as a result of an influenza ("flu") vaccination administered on October 4, 2011. Petition at 2 (ECF No. 1). Respondent argued against compensation, stating that "this case is not appropriate for compensation under the terms of the [Vaccine] Act." Respondent's Report ("Resp. Rept.") at 1 (ECF No. 14).

After carefully analyzing and weighing the evidence presented in this case in accordance with the applicable legal standards, the undersigned finds that Petitioner has failed to provide preponderant evidence that his flu vaccine caused his MS. Thus, Petitioner has failed to satisfy his burden of proof under Althen v. Secretary of Health & Human Services, 418 F.3d 1274, 1280 (Fed. Cir. 2005). Accordingly, the petition must be dismissed.

II. ISSUES TO BE DECIDED

Diagnosis is not at issue; the parties agree that Petitioner's diagnosis is MS, specifically "relapsing remitting [MS]." Joint Prehearing Submission, filed Oct. 20, 2020, at 3 (ECF No. 143). The parties also stipulate that Petitioner received a flu vaccination on October 4, 2011, and presented to the Valley Hospital emergency room ("ER") on November 25, 2011 "for numbness in his arms and neck pain" and "trouble walking." Id. at 1 (citing Petitioner's Exhibit ("Pet. Ex.") 4 at 1129).

Further, "the parties do not dispute the symptomatology [P]etitioner experienced as reported in the medical records, and accordingly, the parties do not anticipate a material factual dispute regarding events reported in the medical records." Joint Prehearing Submission at 3. However, Respondent disputes any suggestion or opinion by Petitioner's treating physicians to the effect "that Petitioner's condition may have been or is vaccine related." Id.

The central dispute is whether Petitioner has provided preponderant evidence of causation for all three Althen prongs. Joint Prehearing Submission at 3. Petitioner asserts that he has proven all three Althen prongs, and Respondent disagrees. Id.

III. BACKGROUND

A. Procedural History

Petitioner filed his petition in April 2014 and medical records in May 2014. Petition; Pet. Exs. 1-10. Respondent filed his Rule 4(c) Report on September 8, 2014, arguing against compensation. Resp. Rept. at 1.

[3] Petitioner also alleged that he was diagnosed with acute disseminated encephalomyelitis ("ADEM") and post-vaccination syndrome in his petition, but subsequently refined his diagnosis to only MS. Petition at 2 (ECF No. 1); Joint Prehearing Submission, filed Oct. 20, 2020, at 3 (ECF No. 143).

The parties filed expert reports from January 2015 to April 2015. Pet. Exs. 11-15;[4] Resp. Exs. A-B. This matter was reassigned to another special master on October 22, 2015. Notice of Reassignment dated Oct. 22, 2015 (ECF No. 33). An entitlement hearing was scheduled to commence on March 6, 2017. Prehearing Order dated June 9, 2016 (ECF No. 41). However, the hearing was adjourned because Petitioner released one of his experts from appearing in this matter and Petitioner required additional time to retain a new expert. Status Conference Order dated Mar. 6, 2017, at 1-2 (ECF No. 50).

In June 2017, Petitioner filed an expert report from Dr. Allen Rosenspire. Pet. Ex. 105. This matter was reassigned to a new special master in June 2017. Notice of Reassignment dated June 20, 2017 (ECF No. 82). On October 6, 2017, Respondent filed a responsive expert report from Dr. David Alexander and an expert report from Dr. S. Michael Phillips. Resp. Exs. E-F. Petitioner filed a supplemental expert report from Dr. Rosenspire on March 16, 2018. Pet. Ex. 107.[5]

Thereafter, an entitlement hearing was scheduled for September 2019. Amended Hearing Order dated Aug. 10, 2018 (ECF No. 99). However, because one of Respondent's experts "could no longer . . . serve as an expert in this case due to a serious medical condition," the hearing was rescheduled for June 2020. Hearing Order dated Aug. 20, 2019, at 1 (ECF No. 106).

In November 2019, Respondent filed an expert report from Dr. S. Mark Tompkins.[6] Resp. Ex. J. Petitioner filed expert reports from Dr. Rosenspire in March and April 2020. Pet. Exs. 120-21. The case was reassigned to the undersigned on May 28, 2020. Notice of Reassignment dated May 28, 2020 (ECF No. 128). The undersigned held a status conference on June 1, 2020. Order dated June 1, 2020 (ECF No. 129). The parties indicated they wished to move the June 2020 entitlement hearing, and therefore, the entitlement hearing was cancelled and rescheduled for February 2021. Id. at 1; Prehearing Order dated June 3, 2020 (ECF No. 130).

Respondent filed a supplemental expert report from Dr. Tompkins on September 1, 2020. Resp. Ex. M. On February 8, 2021, Petitioner filed a motion to continue the February 2021 entitlement hearing because he was unable to reach his expert. Order Granting Continuance

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[4] Petitioner did not rely on these expert reports at the hearing and advised these reports did not need be addressed or considered by the undersigned. Joint Status Rept., filed Jan. 17, 2023, at 2-3 (ECF No. 208).

[5] Petitioner also filed an expert report from Dr. Leslie Hutchinson on this date; however, Petitioner indicated that this report "[did] not need to be considered" by the undersigned. Joint Status Rept. at 3.

[6] Respondent also filed an expert report from Dr. Alan Ducatman in November 2019. Resp. Ex. H. However, Respondent indicated the undersigned did not need to address Dr. Ducatman's reports because "the reports largely addressed issues . . . not discussed by either party at the entitlement hearing," and "the epidemiology discussed in the reports is largely duplicative of the epidemiology discussed in other reports." Joint Status Rept. at 2.

dated Feb. 8, 2021 (ECF No. 153). The undersigned granted Petitioner's continuance and cancelled the hearing. Id.

Petitioner retained a new expert, Dr. Todd Samuels, and filed his expert report on August 19, 2021. Pet. Ex. 127. Respondent filed responsive expert reports from Dr. Tompkins and Dr. Alexander in October 2021. Resp. Exs. N-O. An entitlement hearing was scheduled to begin on December 6, 2022. Prehearing Order dated Nov. 2, 2021 (ECF No. 176). Petitioner filed a supplemental expert report from Dr. Samuels on January 5, 2022. Pet. Ex. 130. On March 12, 2022, Petitioner filed updated medical records. Pet. Ex. 131.

An entitlement hearing was held from December 6 to 8, 2022. Order dated Dec. 8, 2022 (ECF No. 202). Petitioner, Dr. Rosenspire, Dr. Tompkins, Dr. Samuels, and Dr. Alexander testified at the hearing. Transcript ("Tr.") 3, 126, 169. In January 2023, Petitioner filed a supplemental expert report from Dr. Rosenspire and Respondent filed a supplemental expert report from Dr. Tompkins. Pet. Ex. 133; Resp. Ex. R. The parties also filed a joint status report in January 2023, indicating which expert reports the undersigned should consider in determining entitlement. Joint Status Rept., filed Jan. 17, 2023 (ECF No. 208) (indicating the undersigned should consider the expert reports of Dr. Alexander, Dr. Tompkins, Dr. Phillips, Dr. Rosenspire, and Dr. Samuels); see Pet. Exs. 105, 107, 120-21, 127, 130, 133; Resp. Exs. A, E-F, J, M-O, R.

This matter is now ripe for adjudication.

B. Factual History

1. Stipulated Facts

The parties have agreed to the following stipulated facts in their Joint Prehearing Submission. See Joint Prehearing Submission at 1-3.

On October 4, 2011, at 57 years of age, Petitioner received a flu vaccination at his place of employment. Joint Prehearing Submission at 1 (citing Resp. Ex. C at 1). "As of November 2, 2011, [P]etitioner had a two-to-three week history of cough and sore throat that was getting worse." Id. (citing Pet. Ex. 10 at 472). Petitioner presented to urgent care on November 14, 2011 for "hand tremors" for one month and sharp bilateral ear pain for one to two days. Id. (citing Pet. Ex. 10 at 468-69).

On November 25, 2011, Petitioner presented to Valley Hospital ER with complaints of numbness in arms, neck pain, and trouble walking. Joint Prehearing Submission at 1 (citing Pet. Ex. 4 at 1129). Petitioner was examined by neurologist Dr. Vankat Veerappan on November 29 for difficulty balancing, and Dr. Veerappan directed Petitioner's admission for magnetic resonance imaging ("MRI") and lumbar puncture. Id. at 1-2 (citing Pet. Ex. 4 at 392). Petitioner was admitted on November 30, 2011. Id. at 2. Dr. Veerappan re-examined Petitioner on December 1, 2011 for a ten-day history of bilateral upper extremity numbness and ataxia. Id. at 2 (citing Pet. Ex. 4 at 869-70). An MRI conducted on December 1, 2011 showed findings "compatible with active enhancing demyelinating plaques in the lower cervical and upper

thoracic cord extending from C6/7 to T1/2." Id. (quoting Pet. Ex. 4 at 1021). Petitioner was discharged home on December 4, 2011. Id. (citing Pet. Ex. 4 at 950).

Petitioner returned to Dr. Veerappan on December 13, 2011 for balance difficulties and a history of pain and numbness in his arms that started at his neck. Joint Prehearing Submission at 2 (citing Pet. Ex. 8 at 393). Petitioner was re-hospitalized at Valley Hospital that day. Id. (citing Pet. Ex. 4 at 680). Internist Dr. Paul Kalekas documented Petitioner woke up that morning with "'pain down to [the] posterior aspect of both of his arms' and finger paresthesias (fourth and fifth digits)." Id. (quoting Pet. Ex. 4 at 680). Petitioner's "pain subsided," but he still saw Dr. Veerappan that day, and a decision was made to admit Petitioner. Id. (citing Pet. Ex. 4 at 680). Petitioner was transferred to acute rehabilitation on December 20, 2011. Id. (citing Pet. Ex. 4 at 722).

Petitioner sought a second opinion with neurologist Dr. Timothy West at Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada on May 14, 2012. Joint Prehearing Submission at 2 (citing Pet. Ex. 6 at 250). Petitioner reported "numbness across his chest, a feeling of buzzing in his back, numbness across the buttocks area, and weakness in his legs with spasticity." Id. (citing Pet. Ex. 6 at 250-51). Petitioner used a walker for his imbalance and had issues with fatigue. Id. (citing Pet. Ex. 6 at 251). Dr. West reviewed Petitioner's April 2012 MRIs that showed lesions in his brain and spine. Id. (citing Pet. Ex. 6 at 252).

"The parties agree[d] that [P]etitioner has a demyelinating disease now classified as relapsing remitting [MS]." Joint Prehearing Submission at 3.

2. Summary of Medical Records[7]

Prior to Petitioner's flu vaccination, his medical history included hypertension and chronic obstructive pulmonary disease ("COPD") "related to industrial exposure to many chemicals." Pet. Ex. 2 at 37 (follow-up for hypertension); Pet. Ex. 3 at 68 (COPD).

On October 4, 2011, Petitioner received a flu vaccination at his place of employment at 57 years of age. Resp. Ex. C.

On November 2, 2011, Petitioner was seen in an urgent care clinic for a two- to three-week history of a cough and sore throat that was getting worse. Pet. Ex. 10 at 472. The chief complaint was "congestion, sinus pressure x 12 days, 'nervousness' 10/20/2011." Id. at 471. The impression was an upper respiratory infection ("URI") and Petitioner was advised to follow-up with primary care. Id.

[7] This summary of medical records is taken directly from Respondent's Prehearing Brief. See Resp. Prehearing Brief ("Br."), filed Nov. 15, 2022 at 5-8 (ECF No. 198). Petitioner provided a similar summary of the records, but did not provide record citations; therefore, the undersigned has used the summary provided by Respondent, which the undersigned finds to be an accurate summary of the relevant records.

On November 14, 2011, Petitioner was seen in the urgent care clinic for "hand tremors" of a month's duration. Pet. Ex. 10 at 469. He also complained of sharp ear pain in both ears of a one- to two-day duration. Id. at 468. He was previously scheduled to see his primary care physician in January, and the recommendation was to follow up with primary care and neurology. Id. Over-the-counter allergy medication was also directed. Id.

On November 25, 2011, Petitioner presented to the Valley Hospital ER for numbness in his arms and neck pain and trouble walking. Pet. Ex. 4 at 1129. The assessment was a central sensory radiculopathy. Id. at 1134. On November 29, 2011, Petitioner was examined by a neurologist, Dr. Veerappan, for balance difficulty, and the assessment was ataxia, questionable MS, and a cervical myelopathy. Pet. Ex. 8 at 391-92. Dr. Veerappan directed Petitioner's admission to the hospital for MRIs and a lumbar puncture. Id. at 392.

Petitioner was admitted to Valley Hospital on November 30, 2011, and it appears that Dr. Veerappan re-examined him on December 1, 2011 for bilateral upper extremity numbness and ataxia. Pet. Ex. 4 at 869-70. The numbness and ataxia began about ten days previously, and laboratory testing was ordered. Id. An MRI that day showed findings "compatible with active enhancing demyelinating plaques in the lower cervical and upper thoracic cord extending from C6/7 to T1/2." Id. at 1021. Petitioner was discharged home on December 4, 2011 with the diagnoses of bilateral upper extremity paresthesias, cervical spine foraminal stenosis, ataxia, and hypertension. Id. at 949. His MS panel was still pending. Id. at 950.

On December 13, 2011, Petitioner saw Dr. Veerappan for balance difficulties and a history of pain and numbness in his arms, starting at his neck. Pet. Ex. 8 at 393. The assessment was ataxia, MS, paresthesias, and a questionable "[p]ost vaccination syndrome/ADEM." Id. at 394. That same day, Petitioner was re-hospitalized at Valley Hospital. Pet. Ex. 4 at 680. An internist, Dr. Kalekas, noted that Petitioner had awoken that morning with "pain down to [the] posterior aspect of both of his arms" and finger paresthesias (fourth and fifth digits). Id. The pain subsided, but Petitioner went to see Dr. Veerappan, and the decision was made to admit Petitioner to the hospital. Id. Petitioner stated that "he believe[d] this issue originated from the vaccine[] he took on October 4, 2011." Id. "[H]e was asymptomatic until October 13, 2011, after which time he began to have a cold with cough type illness. Then after Thanksgiving, [his] symptomology changed, once again [he] was experiencing ataxia . . . ." Id.

Also on December 13, 2011, Dr. Veerappan re-examined Petitioner at the hospital; the impression was MS exacerbation, questionable post-vaccination syndrome, ADEM, paresthesias of bilateral upper extremities, gait ataxia, and hypertension. Pet. Ex. 4 at 644-45. On December 20, 2011, he was transferred for acute rehabilitation with a transfer diagnosis including "[b]ilateral upper extremity pain and paresthesias secondary to [MS] versus [ADEM] versus post vaccination syndrome." Id. at 722.

On May 14, 2012, Petitioner sought a second opinion regarding his condition at the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada, from neurologist Dr. Timothy West. Pet. Ex. 6 at 250. At that time, Petitioner had numbness across his chest, a feeling of buzzing in his back, numbness across the buttocks area, and weakness in his legs with spasticity. Id. at 250-51. He used a walker to help with imbalance and had fatigue issues. Id. at

251. Dr. West reviewed recent MRIs, performed in April 2012, that showed lesions in the brain and spine. Id. at 252. Dr. West concluded that Petitioner's "clinical history and examination are consistent with a diagnosis of aggressive relapsing remitting [MS]." Id. at 253. Following additional testing, the diagnosis of MS was confirmed, and treatment for MS, particularly ongoing inflammation in Petitioner's brain, was commenced. Id. at 262.

On July 13, 2012, Petitioner presented to the hospital for general weakness, fatigue, and urinary frequency. Pet. Ex. 4 at 146. A history of a diagnosis of MS in November 2011 was noted, and the assessments were diabetes mellitus ("newly diagnosed"), urinary tract infection, MS, acute kidney injury, and a history of hypertension. Id. at 147.

As of December 15, 2021, Petitioner's medications included Copaxone for MS and gabapentin. Pet. Ex. 131 at 2. He reported feeling off balance at times but "ha[d] more control over it," as well as "[o]ccasional pain in his neck, back, and arms." Id. On review of systems, he endorsed tightness in his legs, knees, and ankles, "numbness and tingling along the little finger," and "numbness on the lateral aspect of the feet." Id. Petitioner used a walker when not in his house. Id. at 3.

3. Dr. West's Letter

Dr. West wrote a letter, dated July 15, 2023, stating that Petitioner "suffers from a chronic and progressive neurological disease known as [MS]." Pet. Ex. 6 at 350. He continued, "It is my opinion that to a reasonable degree of medical certainty, the flu vaccine that he was given on October 4, 2011 led to the onset of this central nervous system [("CNS")] demyelinating disease." Id. Dr. West did not explain the basis for his opinion.

4. Petitioner's Hearing Testimony

Petitioner testified that prior to the flu vaccination at issue, he was healthy and active, and had no neurological issues. Tr. 5-6. He had high blood pressure, for which he was taking medication and it was under control. Tr. 6. As part of his employment as an industrial hygienist, he was potentially exposed to chemicals that affected his lungs, leading to a reference to COPD in his medical history. Tr. 18.

On October 4, 2011, Petitioner received a flu vaccination. Tr. 9. Around nine days later, on approximately October 13, Petitioner noticed his hands began twitching. Tr. 9-10. He began to develop stiffness in his neck and pain in his shoulders and ears. Tr. 10. By Thanksgiving 2011, Petitioner was unable to run or jog and he could "barely walk" because he was "wobbling." Id.

Petitioner's condition was getting progressively worse and he presented to neurologist Dr. Veerappan and Valley Hospital ER. Tr. 10-11. Petitioner was admitted to Valley Hospital on November 30, 2011. Tr. 13. Dr. Veerappan could not specify the exact neurological condition Petitioner had, and he referred Petitioner to neurologist Dr. West. Tr. 11-12. Dr. West told Petitioner he had a demyelinating disease of the CNS, which he referred to as MS, although it was not a classic case of MS. Tr. 12.

Since developing MS, Petitioner has continued to have numbness, pain, balance issues, fatigue, shortness of breath, pressure in his abdomen and sometimes his chest, difficulty urinating and defecating, memory issues, vision problems, "problems sitting on hard surfaces for long periods of time," muscle weakness, joint stiffness, tightness in feet and ankles, skin dryness particularly in the legs, difficulty stooping or bending, sleep apnea, bed wetting, erectile dysfunction, and the feeling that "[his] body is too heavy for [his] frame." Tr. 14-15. As of the date of his testimony at the entitlement hearing, December 6, 2022, Petitioner was able to walk but continued to have issues with walking and with his gait. Tr. 15. During the course of his treatment, he was prescribed prednisone for treatment and subsequently developed prednisone-induced diabetes. Id.

C. Expert Reports[8]

1. Petitioner's Expert, Dr. Alan Rosenspire, Ph.D.[9]

a. Background and Qualifications

Dr. Rosenspire received a B.S. in physics from the State University of New York ("SUNY") at Stoneybrook and a Ph.D. in biophysical science from SUNY at Buffalo. Pet. Ex. 106 at 2; Tr. 23-24. He then completed a one-year post-doctoral fellowship in the Department of Microbiology at SUNY Buffalo studying cellular immunology and a three-year post-doctoral fellowship at the Sloan Kettering Institute in New York in the immune biology program. Tr. 24. Dr. Rosenspire has spent his career teaching and conducting research in immunology. Tr. 25-26. He has also served on various editorial boards, including Frontiers of Immunology and Environmental Aspects of Autoimmune Disease. Tr. 27. This was Dr. Rosenspire's first time serving as an expert witness. Tr. 25.

[8] During litigation, both parties submitted several reports by experts who did not testify at the hearing. Prior to submitting the case to the undersigned for adjudication, the parties specifically identified the expert reports and opinions they wanted the undersigned to consider. Joint Status Rept. at 1-3. Petitioner requested that the expert reports of Dr. Rosenspire and Dr. Samuels be considered. Id. at 2 (citing Pet. Exs. 105, 107, 120-21, 127, 133). Petitioner believed Dr. Veerapan's report (Pet. Ex. 11) did not need to be addressed and advised that the reports of Dr. Hua (Pet. Ex. 13) and Dr. Hutchinson (Pet. Ex. 108) did not need to be considered. Id. at 2-3. Respondent requested the undersigned consider the expert reports of Dr. Alexander, Dr. Tompkins, and Dr. Phillips. Id. at 1-2 (citing Resp. Exs. A, E-F, J, M-O). Respondent advised that the expert reports from Dr. Ducatman (Resp. Exs. H, L) did not need to be considered. Id. at 2.

[9] Dr. Rosenspire testified at the hearing and submitted five expert reports. Tr. 3; Pet. Exs. 105, 107, 120-21, 133. At the hearing, none of the experts offered any opinions about mercury or thimerosal. See Joint Status Rept. at 2. Thus, the undersigned did not discuss Dr. Rosenspire's opinions or theories based on mercury or thimerosal in his expert reports.

b. Opinion

i. Althen Prong One

Dr. Rosenspire began by defining MS as a "chronic degenerative disease of the [CNS]." Tr. 36. He explained that it is an autoimmune illness, in that the lesions of MS "are caused by the immune system attacking the nerves in the [CNS]." Tr. 32. More specifically, he opined that the illness is caused when "the immune system attacks the myelin surrounding nerves fibers" and "the nerve fibers themselves." Tr. 36. Symptoms of MS include fatigue; numbness and tingling of the face, arms, fingers, legs, and toes; spasticity; vision issues; bladder and bowel problems; and dizziness and vertigo. Id.; see also Pet. Ex. 21 at 2 (explaining that patients with MS generally "develop an array of symptoms ranging from visual impairment, motor weakness, and sensory disturbances to fatigue, incoordination, cognitive and psychiatric symptomatology, and sphincteric dysfunction, leading gradually to significant neurological disability").[10]

There are two clinical types of MS: relapsing remitting MS and primary progressive MS. Pet. Ex. 21 at 2. Most patients suffer from the relapsing type. Id. According to Dr. Rosenspire, MS usually begins in the age range of "mid-twenties to thirties." Tr. 36. Onset "after 50 is infrequent," and referred to as "late onset."[11] Tr. 37; see also Pet. Ex. 21 at 2-3 (noting studies "have reported [that] first presentation of MS after the age of 50 to be in the range of 1.1% to 10.0%"). There is a difference of opinion about whether there are any significant differences between prognosis or disability in those with late-onset MS compared with those diagnosed with MS at a younger age. See Pet. Ex. 21 at 3. To resolve this question, Polliack et al. studied 640 MS patients, and of those, 30 (4.6%) had been diagnosed with late-onset MS. Id. All of the patients aged 54 or older had a progressive course. Id. Late-onset patients also showed a faster progression to disability than younger patients, as well as a common presentation of depression. Id. at 4. However, "the pattern of disease progression in late-onset MS [was] similar to that observed in younger adults." Id. The authors did not discuss differences in etiology or pathophysiology between younger-onset and late-onset MS. See id. at 3-4.

Regarding etiology of MS, Dr. Rosenspire acknowledged that the cause of MS "remain[s] in question." Pet. Ex. 105 at 3. He opined, however, that the cause "is generally thought to be multifactorial, . . . triggered in a genetically susceptible individual by a combination of one or more environmental factors." Id. He noted that viral infections may be an environmental factor, although he agreed that no specific virus had been linked to the development of MS. Id.

[10] Michael Leon Polliack et al., Late-Onset Multiple Sclerosis, 49 J. Am. Geriatrics Soc'y 168 (2001).

[11] Petitioner filed several articles discussing late-onset MS. See, e.g., Pet. Ex. 20 (Afsaneh Shirani et al., Multiple Sclerosis in Older Adults: The Clinical Profile and Impact of Interferon Beta Treatment, 2015 BioMed Rsch. Int'l 1); Pet. Ex. 21; Pet. Ex. 22 (M. Arias et al., Late Onset Multiple Sclerosis, 26 Neurología 291 (2011)); Pet. Ex. 23 (V. Martinelli et al., Late Onset Multiple Sclerosis: Clinical Characteristics, Prognostic Factors and Differential Diagnosis, 25 Neurological Scis. S350 (2004)).

Regardless, he opined that "epidemiological evidence had clearly demonstrated that [flu] infections are associated with exacerbation and relapse . . . in those [] afflicted with MS." Id.

The causal mechanism that Dr. Rosenspire posited as relevant in MS is molecular mimicry. Tr. 29. He defined molecular mimicry as the "sharing of molecular structures between genetically different organisms" that "occurs when peptides from a pathogen share sequences or structural similarities of proteins of the pathogen's host." Tr. 31. He also opined that molecular mimicry is the mechanism that explains the association between flu viral infection and MS. Id.

In support of his theory of molecular mimicry, Dr. Rosenspire cited a 2007 article by Libbey et al.[12] Pet. Ex. 28. Libbey et al. stated that "[t]he etiology of MS is unknown." Id. at 2. They added that although "many viruses have been shown to be associated with MS, no one virus has ever been demonstrated to be the cause of MS." Id. As for molecular mimicry, they explained that it "is one hypothesis put forth which could reconcile the diverse pathology and etiology of MS." Id. However, Libbey et al. also acknowledged that "[m]olecular mimicry alone may not be able to induce disease; priming of the immune system by infection with a pathogen that carries a molecular mimic to self may have to be followed by a later nonspecific immunologic challenge in order for the disease to be initiated." Id. The authors discussed alternate hypotheses, including the déjà vu theory.[13] Id. at 6. After a review of the current knowledge and studies, including their own studies, the authors concluded that "it has yet to be shown that a single molecular mimic is responsible for initiation of disease."[14] Id. at 16.

After citing to Libbey et al., Dr. Rosenspire opined that MS is "mediated primarily by CD8 lymphocytes, although there are bystander effects."[15] Tr. 32. Dr. Rosenspire testified that the innate immune system also plays a role in the development of the disease. Id. He testified that while there is "no controversy" that the illness is "mediated by the immune system," there is "uncertainty" about what "starts the process going." Tr. 32-33. Moreover, there is a "genetic

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[12] Jane E. Libbey et al., Molecular Mimicry in Multiple Sclerosis, 79 Int'l Rev. Neurobiology 127 (2007).

[13] The déjà vu theory posits "an initial (fetal or neonatal) viral infection that persists and primes the individual for autoimmune disease provided a subsequent infection shares T-cell epitopes with the persisting virus." Pet. Ex. 28 at 6.

[14] Instead, Libbey et al. theorized that the cause of autoimmune illnesses may be "a combination of molecular mimicry, bystander activation, epitope spreading, and heterologous immunity." Pet. Ex. 28 at 16.

[15] Bystander activation is the "indirect or non-specific activation of autoimmune cells caused by the inflammatory environment present during infection. A domino effect can occur, where the non-specific activation of one arm of the immune system leads to the activation of other arms." Pet. Ex. 126 at 2 (A.M. Ercolini & S.D. Miller, The Role of Infections in Autoimmune Disease, 155 Clinical & Experimental Immunology 1 (2008)). For a discussion of the relevant mechanisms, including molecular mimicry, epitope spreading, and bystander activation, see Pet. Ex. 126. Respondent's expert, Dr. Tompkins, also cited this article. See Resp. Ex. J, Tab 5.

component" and an "environmental component[]" to the illness, with "probably" 60% environmental and 40% genetic. Tr. 33.

As further explained by Dr. Rosenspire, "[i]n a normally functioning immune system, B and T lymphocytes are constantly being randomly generated." Pet. Ex. 105 at 3. Some of these cells "recognize pathogenic antigens, and they function to coordinate an attack . . . to destroy recognized pathogenic organisms. Others have the capacity to recognize self-antigens, i.e. they are autoreactive." Id. In the normal healthy immune system, the "autoreactive lymphocytes are held in check by processes collectively known as tolerance." Id. But in autoimmune illnesses, "there is a failure of tolerance," and the autoreactive cells "attack and destroy self-cells and tissue architecture." Id. Dr. Rosenspire stated that in MS, the neurons, their myelin sheaths, and the myelin producing oligodendrocytes of the CNS are attacked. Id.

Dr. Rosenspire suggested there is "direct experimental support" of a link between a flu infection and MS via molecular mimicry. Pet. Ex. 105 at 5. He asserted that "a CD4+ T-cell clone derived from a MS patient infected with and presumably stimulated by [flu] was specific for . . . the [flu] virus hemagglutinin peptide" that "exhibited cross reactivity with [three] myelin-derived peptides." Id. In support, Dr. Rosenspire cited a study from Markovic-Plese et al. (2005),[16] which resulted in two findings. Pet. Ex. 37. First, they found that "cross-reactivity at the level of a single [T-cell receptor ("TCR")] likely assures protection against many more than the originally stimulating viral variant." Id. at 8. And secondly, there are "a range of stimulatory self-antigens" that suggest a "potential for cross-reactivity with CNS proteins." Id. The authors noted, however, that molecular mimicry "only leads to autoimmune disease when it takes place in the context of chronic local inflammation, presentation of self-antigens, and the sufficient number of autoreactive T-cells." Id. (internal citations omitted).

Next, Dr. Rosenspire provided that molecular mimicry can cause other autoimmune illnesses, such as Guillain-Barré syndrome ("GBS") and narcolepsy, post-vaccination. Pet. Ex. 105 at 4-5, 10; Pet. Ex. 121 at 3. He opined that GBS and MS are similar in "their pathophysiology" and "with respect to their mutual connection to active [flu] infection through a mechanism based on molecular mimicry." Pet. Ex. 105 at 10. But see Pet Ex. 35 at 3 tbl.1 (noting the difference in host antigens in GBS and MS).[17] Dr. Rosenspire asserted that GBS is analogous to MS, as both are immune-mediated illnesses associated with molecular mimicry, although GBS is a disease of the peripheral nerves, whereas MS involves the CNS. Tr. 38-40.

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[16] Silva Markovic-Plese et al., High Level of Cross-Reactivity in Influenza Virus Hemagglutinin-Specific CD4+ T-Cell Response: Implications for the Initiation of Autoimmune Response in Multiple Sclerosis, 169 J. Neuroimmunology 31 (2005). In the study, a T-cell clone was created from blood cells of an MS patient during an acute respiratory infection with flu-A virus and then biometric databases were used to search for cross-reactive peptides that had a stimulatory potential. Pet. Ex. 37 at 1-5. They found 15 human mimic peptides that were confirmed to be stimulatory and three human myelin mimics. Id. at 5, 6 tbl.2.

[17] C. Wim Ang et al., The Guillain-Barré Syndrome: A True Case of Molecular Mimicry, 25 Trends Immunology 61 (2004).

Dr. Rosenspire added that because GBS has been added to the "vaccine list,"[18] and because GBS has an analogous mechanism (molecular mimicry), molecular mimicry will eventually be accepted as the mechanism for MS. Tr. 39-40. He acknowledged, however, "that I can't say that it's happened yet." Tr. 40.

The second example of molecular mimicry provided by Dr. Rosenspire is based on the work by Luo et al.[19] related to narcolepsy following the flu vaccine. See Pet. Ex. 125. Dr. Rosenspire testified that Luo et al. "provides strong evidence confirming that in some instances, narcolepsy is an autoimmune disease," triggered by "an antigen found in A strains of the [flu] virus." Tr. 53; see also Pet. Ex. 125 at 2. This "same antigen [] was included in the vaccine developed and administered during the 2009-2010 swine flu pandemic, explaining widespread reports of narcolepsy after vaccination." Tr. 53; see also Pet. Ex. 125 at 2. Dr. Rosenspire explained that narcolepsy is "an immune disorder targeting HCRT neurons."[20] Tr. 54 (quoting Pet. Ex. 125 at 2). Luo et al. showed the illness was probably triggered by a "hemagglutinin flu protein" in the vaccine that was homologous with a "protein residing on key brain cells" which induced narcolepsy. Id.; Pet. Ex. 121 at 3; see also Pet. Ex. 125 at 2. Thus, Dr. Rosenspire opined Luo et al. showed that "the [flu] vaccine . . . had the ability to stimulate an autoimmune reaction to [CNS] cells." Tr. 54-55; see also Pet. Ex. 121 at 3. While he acknowledged that these are not the cells that cause MS, Dr. Rosenspire testified that this finding was still important because it was "the first example [that has] actually proved molecular mimicry as a mechanism." Tr. 55. Moreover, Dr. Rosenspire opined that the findings by Luo et al. demonstrated that molecular mimicry is "a proven mechanism" specific to the ability of the flu vaccine to elicit "an autoimmune response to neural antigens." Pet. Ex. 121 at 3. On cross-examination, Dr. Rosenspire agreed that the cross-reactive epitopes in the flu vaccine that he believed cause MS are not known. Tr. 63. He also agreed that the target receptors involved in the pathogenesis of narcolepsy are not involved in causing MS. Tr. 64.

Regarding epidemiology, Dr. Rosenspire agreed that currently, "the weight of epidemiology studies [] support a statistically significant connection of [flu] vaccination to GBS," but not to MS. Pet. Ex. 105 at 5. He emphasized, however, that "lack of epidemiological evidence supporting such a connection should not be confused with evidence against, especially in [] light of a logically self-consistent mechanist[ic] model." Id.

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[18] Although Dr. Rosenspire used the phrase "vaccine list," the context of his reference suggests that he meant "Vaccine Injury Table," where GBS is a recognized injury following flu vaccination for which a Petitioner may be entitled to compensation if certain criteria are met. See 42 C.F.R. § 100.3(a)(XIV)(D).

[19] Guo Luo et al., Autoimmunity to Hypocretin and Molecular Mimicry to Flu in Type 1 Narcolepsy, 115 Proc. Nat'l Acad. Scis. U.S. E12323 (2018). Although Dr. Rosenspire referred to the author of this article as Emmanuel Mignot, the first named author of the paper is Guo Luo. See Pet. Ex. 125.

[20] Hypocretin, or orexin, ("HCRT") "regulat[e] feeding behavior as well as the sleep-wake cycle." Orexin, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=35458 (last visited Aug. 7, 2023); see also Pet. Ex. 125 at 2.

In response to Respondent's experts' reliance on epidemiology to assert that the flu vaccine does not cause MS, Dr. Rosenspire raised several concerns.[21] First, he disagreed that epidemiological studies could speak to causation on an individual level. Tr. 44. He opined that studies may show that the flu vaccine is safe, but they do not allow one to conclude that the vaccine is "safe for everybody." Id. Dr. Rosenspire felt that the Respondent's experts' "reliance on the epidemiological data was misplaced" in this regard. Tr. 46-47. On cross-examination, Dr. Rosenspire agreed that epidemiology has shown that a causal relationship between the flu vaccination and MS is unlikely, but he emphasized that such a relationship was "certainly possible." Tr. 59.

Second, he explained that the "statistical power [of studies] depend[] on how many people you look at," and no study can be "100 percent certain" in its findings. Tr. 48. And third, the epidemiology studies are limited by the fact that the flu vaccine changes every year; every year there are "different antigens" in the vaccine. Tr. 48-49. Dr. Rosenspire opined that because the vaccine differs from year to year, it is "difficult to draw conclusions" using epidemiology studies. Tr. 49. He described it as "comparing apples to oranges." Tr. 48-49.

Further, Dr. Rosenspire took issue with the notion that molecular mimicry is a "completely irrelevant theory."[22] Tr. 45. To illustrate this, before the hearing, Dr. Rosenspire conducted a search in the PubMed database[23] and found over 8,600 references to molecular mimicry. Id. The first reference was in 1979, and in 2022, there were over 200 references to the mechanism. Id. He also noted that the National Institutes of Health ("NIH") established and maintain an epitope database,[24] which "confirm[s] that epitope mimicry is an extraordinarily common and natural phenomenon." Pet. Ex. 107 at 4. For these reasons, Dr. Rosenspire opined that molecular mimicry "is an active . . . fundamental foundation of immunology." Tr. 45.

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[21] For Dr. Rosenspire's discussion of the Institute of Medicine ("IOM") Report, which examined epidemiology studies related to the flu vaccination and MS, and his disagreement with the Respondent's experts' use of the Report, see Pet. Ex. 105 at 5-6.

[22] This paragraph primarily relates to Dr. Phillips' criticism of molecular mimicry. See Resp. Ex. F.

[23] "PubMed is a free resource supporting the search and retrieval of biomedical and life sciences literature . . . . The PubMed database contains more than 35 million citations and abstracts of biomedical literature." Nat'l Libr. Med., Nat'l Ctr. for Biotechnology Info., PubMed Overview, https://pubmed.ncbi.nlm.nih.gov/about/ (last visited Aug. 7, 2023).

[24] For more information on this database, known as the Immune Epitope Database ("IEDB"), see Pet. Ex. 116 (Randi Vita et al., The Immune Epitope Database (IEDB) 3.0, 43 Nucleic Acids Rsch. D405 (2015)); Pet. Ex. 117 (Ward Fleri et al., The Immune Epitope Database: How Data Are Entered and Retrieved, 2017 J. Immunology Rsch. 1); Pet. Ex. 118 (Ward Fleri et al., The Immune Epitope Database and Analysis Resource in Epitope Discovery and Synthetic Vaccine Design, 8 Frontiers Immunology 1 (2017)).

He also disagreed with Respondent's expert, Dr. Phillips' opinion that molecular mimicry is undermined by studies done that show widespread presence of homologies,[25] and the assertion that "if pathogens [] mimicked epitopes, everybody would have autoimmune diseases all the time." Tr. 46. Dr. Rosenspire explained that usually lymphocytes (B and T cells) are under control and do not expand. Id. The abnormal pathology occurs, however, when the lymphocytes, "which recognize self-epitopes, are allowed to expand." Id. One of the reasons this may occur, according to Dr. Rosenspire, is when the immune system is "blast[ed]" with a vaccination, which causes activation of the lymphocytes. Id.

In his second expert report, Dr. Rosenspire refined his theory, stating that "because of molecular mimicry, . . . pre-existing low affinity lymphocytes already reactive to oligodendrocyte proteins may have been provided with substantial higher doses of an eliciting antigen" and once "activated[,] . . . cytotoxic T cells which recognize T cell epitopes on oligodendrocytes appear and begin to attack and destroy oligodendrocytes, just as occurs in MS in the absence of vaccination." Pet. Ex. 107 at 2. He further offered, "after the initial activation of pre-existing low affinity oligodendrocyte reactive lymphocytes, by whatever mechanism, be it molecular mimicry, or the so far undefined mechanism(s) more commonly responsible for the initiation of MS, the subsequent immune and nervous system pathologies are expected to be more or less identical." Id.

In his third expert report, Dr. Rosenspire added another layer to his mechanistic theory, suggesting that the peptides in the flu vaccine need not be exact replicates, but that they could "immunologically resemble . . . molecules expressed on human oligodendrocytes (molecular mimicry)." Pet. Ex. 120 at 2. He further opined that in addition to causing the desired response to vaccination, there was "an unwanted off-target immune response to both T and B cell epitopes . . . against those specific oligodendrocyte membrane proteins" that "initiat[ed] the immunologically mediated destruction of oligodendrocyte membranes." Id.

During the hearing, Respondent's expert, Dr. Tompkins, referenced two papers published in 2022 regarding the association of Epstein-Barr virus ("EBV") and MS.[26] Tr. 98-99 (citing Resp. Exs. P-Q). In Dr. Rosenspire's post-hearing expert report addressing these papers, he

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[25] See Resp. Ex. F, Tab 28 (Mireia Sospedra & Roland Martin, Molecular Mimicry in Multiple Sclerosis, 39 Autoimmunity 3 (2006)); Resp. Ex. F, Tab 29 (Brett Trost et al., No Human Protein Is Exempt from Bacterial Motifs, Not Even One, 1 Self/Nonself 328 (2010)); Resp. Ex. F, Tab 30 (Brett Trost et al., Bacterial Peptides Are Intensively Present Throughout the Human Proteome, 1 Self/Nonself 71 (2010)); Resp. Ex. F, Tab 31 (Darja Kanduc et al., Massive Peptide Sharing Between Viral and Human Proteomes, 29 Peptides 1755 (2008)).

[26] Because the articles had not been filed prior to the hearing, the undersigned did not allow Dr. Tompkins to discuss them at the hearing. Tr. 99-102. The parties agreed that the articles would be filed and addressed in post-hearing expert reports. Tr. 100-02. Dr. Rosenspire addressed the articles in his final expert report. See Pet. Ex. 133 (citing Resp. Ex. P (Kjetil Bjornevik et al., Longitudinal Analysis Reveals High Prevalence of Epstein-Barr Virus Associated with Multiple Sclerosis, 375 Science 296 (2022)); Resp. Ex. Q (Tobias V. Lanz et al., Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNA1 and GlialCAM, 603 Nature 321 (2022))).

acknowledged that they "suggest[] that EBV is the leading cause of MS." Pet. Ex. 133 at 3. Dr. Rosenspire responded by observing that Lanz et al. "explicitly provides evidence that molecular mimicry is the mechanism linking EBV to MS." Id. (citing Resp. Ex. Q at 1). Based on this reference, Dr. Rosenspire argued that molecular mimicry is a relevant causal mechanism to explain how the flu vaccine can cause MS. Id. He also asserted that exposure to EBV is not the only possible cause of MS. Id. He concluded that the articles do not "directly refute the idea" that Petitioner's MS was caused by his flu vaccination. Id. And he suggested that Lanz et al. supports the theory of molecular mimicry as valid in this context and as a "scientifically accepted medical theory." Id.

ii. Althen Prong Two

Dr. Rosenspire opined that "[i]t is more likely than not that . . . [Petitioner's] MS symptoms subsequent to his vaccination . . . [are] an example of a cause and effect relationship." Pet. Ex. 105 at 10. And he found that it was "more likely than not [] the [flu] vaccine was a substantial factor in causing [Petitioner's] MS." Id.

Dr. Rosenspire testified that Petitioner's flu vaccination "preceded his develop[ment] [of] an autoimmune condition diagnosed as [MS]." Tr. 41. The vaccination "activated T or B lymphocytes, which recognize[d] myelin and/or oligodendrocyte membrane cross-reactive epitopes on [flu] viral peptides included in the vaccine. The activation of these autoreactive lymphocytes was then a substantial contributing factor to his autoimmune condition." Id.

One reason why Dr. Rosenspire opined that Petitioner's MS was caused by his flu vaccine is because Petitioner's MS was late-onset, having developed at almost 58 years old, which was "rare." Tr. 33-34; Pet. Ex. 105 at 10; Pet. Ex. 120 at 5-6. Petitioner's age at onset made Dr. Rosenspire "think that maybe there was something to the vaccine being important here." Tr. 34. He also noted that epidemiology studies cited by Respondent's experts either excluded cases with MS onset over 50 years of age or failed to distinguish between those whose symptoms began before or after age 50. Tr. 34, 49; Pet. Ex. 105 at 6; Pet. Ex. 120 at 6. Because these studies did not stratify data based on age, Dr. Rosenspire opined that it was "impossible" to determine whether older patients "reacted differently." Tr. 49.

One of these studies, DeStefano et al. (2003),[27] reported on a case-controlled study using data from three large health maintenance organizations ("HMOs") from 1995 to 1999 in patients ages 18 to 49 with MS or optic neuritis to determine whether vaccination increased the risk of developing these illnesses. Resp. Ex. F, Tab 7 at 1-2. The study included 440 patients with MS (332) or optic neuritis (108) and 950 controls. Id. at 2. Vaccination history was obtained for all participants. Id. The study showed that vaccination did not increase the risk of MS or optic neuritis. Id. at 3. Another study, Hernán et al. (2004),[28] examined the risk of MS following

[27] Frank DeStefano et al., Vaccinations and Risk of Central Nervous System Demyelinating Diseases in Adults, 50 Archives Neurology 504 (2003).

[28] Miguel A. Hernán et al., Recombinant Hepatitis B Vaccine and the Risk of Multiple Sclerosis, 63 Neurology 838 (2004).

vaccination with the recombinant hepatitis B vaccine as well as other vaccines, including the flu vaccine. Pet. Ex. 39 at 2. They found no increased risk of MS after flu vaccination. Id. at 3, 3 tbl.2. Patients with MS age 50 and older constituted 9.2% of the MS patients and 9.7% of the controls. Id. at 3, 3 tbl.1. The authors specifically noted that their results "did not vary significantly by [] age." Id. at 3. Hernán et al., however, did not state the date of onset in patients, including those who were age 50 or older. Id. at 4.

Although Dr. Rosenspire accurately stated DeStefano et al. and Hernán et al. either did not include cases of late-onset MS or did not differentiate between MS cases with onset prior to or after age 50, there was no article or other evidence filed by either party to suggest that late-onset MS patients have an increased risk of developing MS after a flu vaccination or that an MS flare was more likely in the late-onset group. See Pet. Ex. 105 at 6; Tr. 59-60. And on cross-examination, Dr. Rosenspire agreed that there is no known specific difference between the pathogenesis of late-onset MS, as compared to onset in younger patients. Tr. 59-60.

Next, Dr. Rosenspire noted that the epidemiology studies relied upon by the Respondent's experts did not study the same vaccine that Petitioner received, since the vaccines change from year to year. Tr. 49.

Further, Dr. Rosenspire testified that "the response to a vaccine or . . . antigen or pathogen depends on one's genetics," specifically an individual's major histocompatibility complex ("MHC")[29] genotype and in humans, the human leukocyte antigens ("HLA") haplotype.[30] Tr. 50; see also Tr. 60. Based on Petitioner's HLA haplotype, "[t]he probability of anybody in any of the studies having [Petitioner's] haplotype is less than one in 113,000."[31] Tr. 50; see also Pet. Ex. 120 at 6. He testified that the studies relied on by Respondent's experts were done in "predominantly Caucasian populations," in Canada or Europe, and the "HLA haplotype . . . is very different from the distribution of HLA haplotypes in African Americans." Tr. 50. Therefore, Dr. Rosenspire argued that the epidemiology studies do not rule out the

[29] Major histocompatibility complex is "the genes determining the major histocompatibility antigens, in all species a group of closely linked multiallelic genes located in a small region on one chromosome." Major Histocompatibility Complex, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=66341 (last visited Aug. 7, 2023).

[30] Human leukocyte antigens are "histocompatibility antigens governed by genes of the HLA complex (the human major histocompatibility complex), a region on the short arm of chromosome 6 containing several genetic loci, each having multiple alleles." Human Leukocyte Antigens, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=56923 (last visited Aug. 7, 2023). For an explanation of the HLA haplotypes that contribute to MS genetic susceptibility, see Resp. Ex. H, Tab 5 at 2 (Emmanuelle Waubant et al., Environmental and Genetic Risk Factors for MS: An Integrated Review, 2019 Annals Clinical & Translational Neurology 1).

[31] Dr. Rosenspire based his calculation as to probability on the fact that (1) "[Petitioner] is an African American male" and (2) "on several million bone marrow donor samples in the American Bone Marrow Registry." Pet. Ex. 120 at 6.

incidence of MS after vaccination at the individual level. Tr. 50-51. He further testified, "[s]o my guess," which he acknowledged he cannot prove, "is that [Petitioner's] MHC haplotype allowed him to have an autoimmune response to the vaccine." Tr. 60. Dr. Rosenspire opined that "it's possible, conceptually possible, . . . that different vaccines can cause an autoimmune response, but it[] . . . depend[s] on the dosage, . . . past history, and . . . the MHC haplotype of the person . . . inoculated." Tr. 61. "[I]f everything lines up, [] then you may have a case like [Petitioner's] . . . ." Id.

Regarding alternative explanations for the cause of Petitioner's MS, and specifically Dr. Tompkins' suggestion that Petitioner had a URI with symptoms that began on October 13, 2011, Dr. Rosenspire offered two responses. Pet. Ex. 121 at 3-4. First, Dr. Rosenspire opined that there is no evidence that Petitioner was infected with any pathogen that has been causally linked to the onset of an autoimmune illness. Id. at 3. Second, he observed that Dr. Tompkins did not describe a mechanism by which any such pathogen could cause an autoimmune condition. Id. at 4. Additionally, Dr. Rosenspire noted an article from Ercolini and Miller, which Dr. Tompkins used to support his alternative cause opinion, and described molecular mimicry, the theory which Respondent's experts "spent considerable time disparaging."[32] Pet. Ex. 121 at 4 (citing Pet. Ex. 126; Resp. Ex. J. at 11).

iii. Althen Prong Three

In his initial expert report, Dr. Rosenspire opined that Petitioner's symptoms began approximately ten days following his flu vaccination, "within the same time frame that the maximal anti-[flu] response is expected." Pet. Ex. 105 at 10. Dr. Rosenspire failed to explain what symptoms he relied on for this opinion.

At the hearing, Dr. Rosenspire testified that molecular mimicry would result in "an immune response to self-epitopes in two to three weeks," consistent with onset of symptoms in Petitioner's case. Tr. 65-66; see also Pet. Ex. 107 at 2. Dr. Rosenspire did not describe the symptoms which he believed occurred two-to-three weeks after vaccination.

2. Petitioner's Expert, Dr. Todd L. Samuels, M.D.[33]

a. Background and Qualifications

Dr. Samuels is a board-certified neurologist. Pet. Ex. 129 at 2. After receiving his M.D. from Pennsylvania State University in 1985, he completed an internship in internal medicine and psychiatry at George Washington University Medical Center and a neurology residency at Georgetown University Hospital. Id. at 2-3. Since 1989, Dr. Samuels has worked as a

[32] Respondent's expert, Dr. Phillips was the most critical of the theory of molecular mimicry. For his opinions about molecular mimicry, see Resp. Ex. F at 18-21.

[33] Dr. Samuels provided two expert reports and testified at the hearing. Pet. Exs. 127, 130; Tr. 126.

neurologist at hospitals and in private practice and performs independent medical evaluations. Id. at 1. He is also a member of the American Academy of Neurology. Tr. 128.

b. Opinion

i. Althen Prong One

Dr. Samuels explained that MS is an immune-mediated illness, whereby "[t]here is activation of the immune system where the body recognizes myelin, the coating around nerve cells, as being foreign and the immune system attacks one's own nervous system." Tr. 131-32. "[T]here are two major mechanisms proposed to account for the activation of self-reactive T and B cells and the induction of autoimmunity," namely "molecular mimicry and bystander activation." Pet. Ex. 127 at 2; see also Tr. 131. He defined molecular mimicry as a mechanism whereby "an antigenic epitope . . . that is structurally similar to (mimics) an epitope of a self-molecule has the potential to trigger the activation of self-reactive, naïve T or B lymphocytes." Pet. Ex. 127 at 2-3. Once activated, the cells "expand in number and mature into effector (memory) T cells that have a lower threshold for activation by self-antigens." Id. at 3. The cells "migrate to specific tissues, produce additional mediators/cytokines, and mediate injury on contact with cross-reactive self-antigens." Id.

He defined bystander activation as the process that occurs when "tissue damage from an infection (or an inflammatory process) [] lead[s] to the liberation or exposure of host antigens in a context that allows presentation to, activation of, and expansion of self-reactive lymphocytes." Pet. Ex. 127 at 3. It does not require structural similarity like molecular mimicry. Id.

In support of these two mechanisms, Dr. Samuels quoted a 2004 IOM report,[34] which wrote,

> It is conceivable that vaccine antigens could mimic self (host), that stimulation from vaccines could trigger bystander activation just as an infectious organism does, and that either or both of these potentially damaging mechanisms could possibly lead to the development of central or peripheral demyelinating disease. There is no reason in theory why [flu] virus antigens, or other substances in the vaccines (e.g., residual traces of constituents from the production process), could not function in this way. Thus, there is a theoretical basis for [flu] vaccines to induce immune responses that could possibly lead to demyelination.

Pet. Ex. 127 at 3 (quoting Pet. Ex. 128 at 140). Dr. Samuels noted the report also stated that "[c]entral or peripheral neurological manifestations are not generally a feature of [flu] infection but are observed." Id. (quoting Pet. Ex. 128 at 144). Lastly, as Dr. Samuels quoted, the IOM report concluded "there is a theoretical basis for mechanisms involving immune-mediated processes by which a vaccine could cause neurological complications, including a peripheral demyelinating disease like GBS or a central demyelinating disease like MS. There is no reason,

[34] Inst. of Med., Immunization Safety Review: Influenza Vaccines and Neurological Complications (Kathleen Stratton et al. eds., 2004).

in theory, why [flu] vaccines could not operate in this way." Id. at 3-4 (quoting Pet. Ex. 128 at 145).

On cross-examination, Dr. Samuels testified that he provides care for about 100 patients with MS, and that he recommends that they receive the flu vaccine. Tr. 134-36. He agreed that epidemiology studies recommend that MS patients receive the flu vaccine. Tr. 136. He also agreed that epidemiology studies indicate that it is unlikely there is a relationship between the flu vaccine and MS. Id.

ii. Althen Prong Two

Dr. Samuels testified that "more likely than not that the vaccine caused [Petitioner's] [MS]." Tr. 130. He cited several reasons for this opinion, including the fact that Petitioner was older at the time he developed MS, that Petitioner's initial disease course was aggressive, and that there was a temporal association between vaccination and disease onset. Tr. 131, 139-40. He further testified that Petitioner's course was atypical; the "typical textbook case of MS would be . . . female, in the twenties or thirties, who presents with subtle symptoms," such as "[l]oss of vision in one eye, double vision, numbness or tingling," and balance issues. Tr. 139. Dr. Samuels also testified that Petitioner's thoracic MRI showed a long segment of demyelination, which is not typical. Tr. 140. The typical findings on MRI include plaques in the brain and spinal cord. Id.

At the hearing, Dr. Samuels reviewed Petitioner's MRI reports and provided his opinions about the findings.[35] Petitioner's initial MRI studies, done in December 2011, were discussed first. See Tr. 141-42. The brain MRI was interpreted as showing "a few very small foci of increased signal density demonstrated within the white matter, nonspecific pattern" that "could represent early small vessel disease or possibly a demyelinating process." Id. (quoting Pet. Ex. 4 at 1025). While these findings are "not diagnostic," they are "possibly indicative of MS." Tr. 142. Dr. Samuels was unable to determine the age or onset of the brain abnormalities, opining that there was no way to determine the age of the lesions without a previous study for comparison. Tr. 142-43. However, he believed the findings were consistent with MS due to the clinical report of numbness in Petitioner's arms. Tr. 147.

The December 2011 thoracic MRI was interpreted as showing abnormal enhancement in the thoracic cord from C6/C7 to T1/T2, consistent with active demyelinating plaques. Tr. 144 (citing Pet. Ex. 4 at 1020). Dr. Samuels testified that the enhancement seen in this area of the thoracic cord indicates this was "definitely an acute lesion." Id. He explained that "[e]nhancement by definition is acute," typically weeks old. Tr. 152. He also noted there was a second acute lesion in the thoracic cord from T1/T2 to T3/T4. Tr. 144-45. Thus, based on the reports, there were two lesions, side by side, one extending from C6/C7 to T1/T2, and the second from T1/T2 to T3/T4. Tr. 145. Dr. Samuels opined that it was not clear whether the second of these two lesions was enhanced. Id. He explained that lack of enhancement does not necessarily indicate that the lesions are not active, and the MRI images must be correlated with the patient's

[35] Dr. Samuels reviewed only the MRI reports, not the images, and therefore, his opinions were based only on the reports. See Tr. 140-41.

symptoms. Tr. 146. Lesions in the brain may occur without symptoms, but Dr. Samuels opined that lesions in the spinal cord are "never asymptomatic." Id.

Given the fact that Petitioner did not have MRI studies done before the onset of his symptoms or vaccination, Dr. Samuels opined that there was no way to know whether Petitioner's brain lesions were acute or old. Tr. 146-47. However, based on the enhancement seen in the spinal cord lesions, Dr. Samuels testified that the findings were consistent with a temporal relationship with Petitioner's vaccination. Tr. 152.

Dr. Samuels also reviewed the MRI reports from 2012. See Tr. 155-60. He noted that the MRI findings had improved; there was less enhancement and less demyelination on the June 2012 studies. Tr. 155-57. He also reviewed the 2020 MRI reports, and he opined that there was no significant change in the MRIs compared to 2012. Tr. 163-64. He noted that Petitioner had received aggressive treatment for his MS in this time frame. Tr. 158.

iii. Althen Prong Three

Regarding prong three, Dr. Samuels testified that Petitioner received his flu vaccine on October 4, and developed flu-like symptoms about ten days later. Tr. 131. This was followed by complaints of loss of balance, numbness, clumsiness, and tremors on November 29, 2011. Id. Based on this timeline, and the MRI reports described above, Dr. Samuels opined that there was "a proximate temporal relationship between the [flu] vaccine and [Petitioner's] injury." Pet. Ex. 127 at 4.

3. Respondent's Expert, Dr. Stephen Mark Tompkins, Ph.D.[36]

a. Background and Qualifications

Dr. Tompkins received his B.S. in microbiology from the University of Illinois and a Ph.D. in immunology and molecular pathogenesis from Emory University. Resp. Ex. K at 1; Tr. 70. He then completed two post-doctoral fellowships in immunology where he "studied the features of priming autoreactive T cells using the experimental autoimmune encephalomyelitis ("EAE") mouse model, . . . the Theiler's virus model for induced autoimmune encephalomyelitis," and "priming vaccine-elicited T cell responses against novel [flu] vaccines." Tr. 70. Dr. Tompkins has taught immunology and virology classes to undergraduate, graduate, and veterinary students at the University of Georgia since 2005. Resp. Ex. K at 2; Tr. 71-72. He

[36] Dr. Tompkins submitted four expert reports and testified at the hearing. Resp. Exs. J, M-N, R; Tr. 3. The undersigned did not discuss the aspects of his reports that dealt with mercury, since that issue was not pursued by either parties. Joint Status Rept. at 2. Respondent also submitted the expert report of Dr. Phillips. See Resp. Ex. F. In the parties' joint status report, Respondent stated that "Dr. Phillips was originally [R]espondent's expert immunologist, but for personal reasons, could no longer participate in Vaccine Program cases. Respondent's replacement immunologist, Dr. Tompkins, discusses Dr. Phillips' initial report." Joint Status Rept. at 2. For the sake of brevity, the undersigned does not summarize or discuss Dr. Phillips' expert report, as the substance of that report was generally covered by Dr. Tompkins.

is also the Director of a Center for Excellence for Flu Virus Research and Response. Resp. Ex. N at 1; Tr. 72, 75-76. Although he currently does work related to animal diseases, he also assesses human vaccines and antiviral drugs and other treatments or preventatives for respiratory infection. Tr. 73. Over the course of his career, Dr. Tompkins has published over 100 peer-reviewed publications in the fields of immunology and virology. Resp. Ex. K at 23-33; Resp. Ex. N at 1.

b. Opinion

i. Althen Prong One

Dr. Tompkins opined that "the [flu] vaccine was not related to the onset of clinical symptoms that were ultimately diagnosed as [MS]." Tr. 79. His opinions were based on a "significant body of data around the [flu] vaccine and [MS]" showing "no association between . . . the [i]nactivated flu vaccine[] and onset of [MS]." Tr. 80.

In support of his opinion, Dr. Tompkins cited several articles. The first, by Hapfelmeier et al.,[37] was published in 2019 and based on a large data set. Tr. 80 (citing Resp. Ex. H, Tab 10). The study looked at "the ambulatory claims data of the Bavarian Association of Statutory Health Insurance Physicians covering 2005-2017 . . . and vaccinations in the [five] years before first diagnosis." Resp. Ex. H, Tab 10 at 1. The MS patients totaled 12,262, and controls included patients with Crohn disease (19,296), psoriasis (112,292), and those with no history of autoimmune diseases (79,185), for a total of 210,773 controls. Id. The research showed that vaccination was not associated with a risk of developing MS. Id.

The second paper, authored by Mailand and Fredriksen,[38] was a literature review published in 2017 that provided a summary of "all existing knowledge about vaccines and MS" relative to whether vaccines are "a predisposing factor for developing MS" and "[t]he impact of vaccines on disease progression and risk of relapse." Resp. Ex. H, Tab 2, at 1. Fifty-one articles were reviewed, and several vaccines, including the H1N1 and seasonal flu vaccines, were discussed. Id. at 2. The risk of MS after H1N1 and/or flu vaccination was the subject of six studies, and none of these studies found an increased risk of MS after vaccination. Id. Regarding the risk of relapse, one of 14 studies identified "found an increased tendency to relapse ([three] weeks after vaccination against [flu])." Id. The other 13 papers reported "no increased risk of relapse following vaccination against seasonal [flu] or H1N1."[39] Id. The

[37] Alexander Hapfelmeier et al., A Large Case-Control Study on Vaccination As Risk Factor for Multiple Sclerosis, 93 Neurology E908 (2019).

[38] Mia Topsøe Mailand & Jette Lautrup Fredriksen, Vaccines and Multiple Sclerosis: A Systematic Review, 264 J. Neurology 1035 (2017).

[39] The authors noted their limitations, including the fact that "there [was] over 40 years between the oldest and newest studies," and the vaccines studied differed over that period, "making it problematic to summarize the findings and make a final conclusion." Resp. Ex. H, Tab 2, at 12.

authors concluded that the seasonal flu vaccinations "do not seem to increase the risk of developing MS" or "have a negative effect on disease progression." Id. at 14.

At the hearing, Dr. Tompkins also cited to Bardage et al. (2011),[40] which reported on a Swedish population-based study conducted from October 2009 to March 2010 that examined the risk of neurological and autoimmune illnesses after vaccination against flu A (H1N1). Tr. 81; Resp. Ex. F, Tab 9 at 1-2. The study population consisted of both vaccinated (52.6% or 1,024,019) and unvaccinated people in Stockholm County, a population comprised of 1.98 million. Resp. Ex. F, Tab 9 at 2. They found no increased risk of MS. Id. at 4.

While Dr. Tompkins agreed that "clinical trials may be too small to reveal a rare event such as MS," he emphasized that "there is still no positive evidence." Resp. Ex. J at 7. In summary, Dr. Tompkins testified that epidemiological studies, including those from Hapfelmeier et al., Mailand and Fredriksen, and Bardage et al., do not show any association between flu vaccination and MS. Tr. 81-82; see also Resp. Ex. J at 6-7; Resp. Ex. J, Tab 6.[41] Further, he testified that there is no reason why the results of these studies are inapplicable here. Tr. 82.

Next, Dr. Tompkins opined that there is no evidence that the flu vaccine increases the risk of flares or relapses in patients with MS, and he cited literature in support. Tr. 83; see also Resp. Ex. F, Tab 12 at 3 ("Several early case reports [] suggested that relapse or onset of MS [could] follow vaccination against [flu];" however, "carefully controlled studies have not demonstrated an increase in relapse rate or progression of disability following [flu] vaccination.");[42] Resp. Ex. F, Tab 13;[43] Resp. Ex. F, Tab 16;[44] Resp. Ex. F, Tab 17.[45] De Keyser et al. (1998),[46] for example, found that the rate of flares was comparable in vaccinated and

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[40] Carola Bardage et al., Neurological and Autoimmune Disorders After Vaccination Against Pandemic Influenza A (H1N1) with a Monovalent Adjuvanted Vaccine: Population Based Cohort Study in Stockholm, Sweden, 343 BMJ 1 (2011).

[41] Eric M.L. Williamson et al., Vaccines in Multiple Sclerosis, 16 Current Neurology & Neuroscience Reps. 1 (2016).

[42] Douglas R. Jeffrey, The Use of Vaccinations in Patients with Multiple Sclerosis, 19 Infectious Med. 73 (2002).

[43] Christian Confavreux et al., Vaccinations and the Risk of Relapse in Multiple Sclerosis, 344 New Eng. J. Med. 319 (2001).

[44] A.E. Miller et al., A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Influenza Immunization in Multiple Sclerosis, 28 Neurology 312 (1997).

[45] Eitan Auriel et al., Seasonal and H1N1v Influenza Vaccines in MS: Safety and Compliance, 314 J. Neurological Scis. 102 (2012).

[46] Jacques De Keyser et al., Effects of Influenza Vaccination and Influenza Illness on Exacerbations in Multiple Sclerosis, 159 J. Neurological Scis. 51 (1998).

unvaccinated MS patients. Resp. Ex. F, Tab 15 at 1-2; Tr. 83-84. They also found there was a greater risk of exacerbations in patients with flu-like illnesses as compared with the vaccinated population. Resp. Ex. F, Tab 15 at 1-2; Tr. 83-84. Of note, Dr. Tompkins testified this study appeared to show vaccination "reduced the likelihood of having a flare," suggesting "there might be a benefit" to vaccination. Tr. 84; see also Resp. Ex. J, Tab 9 at 1 ("Clinicians should recommend that patients with MS receive the [flu] vaccination annually.").[47] Farez et al. (2012)[48] examined whether the H1N1 flu vaccination caused exacerbations in 137 relapsing-remitting MS patients, 60 (44%) of which were vaccinated against H1N1. Resp. Ex. F, Tab 18 at 1. They found no association between flu vaccination and increased exacerbation rate in MS. Id. at 2.

Next, Dr. Tompkins opined that it was unlikely that molecular mimicry is a mechanism by which the flu vaccine could cause MS.[49] Tr. 89-91. Although research shows that the incidence of shared homology is very high, there is no "rampant autoimmune illness," and therefore, "there must be other features that are actually driving the potential for an autoimmune response other than just having a mimic that will cross react." Tr. 90. In the case of autoimmune illness following infection, the additional feature is the damage to the host from the infection, "independent of any homology within a pathogen." Tr. 90-91. However, he opined this is a feature not necessarily seen with vaccines. Tr. 91.

In the classic EAE model, an inflammatory adjuvant was used to trigger inflammation, but the flu vaccine here did not contain an adjuvant. Tr. 91. Further, Dr. Tompkins opined that "there is very little [] evidence to show that there are homologies between th[e] [flu] vaccine and epitopes in the [CNS][50] that are associated with [MS]." Id. Dr. Tompkins found it was inappropriate to use GBS as an analogy for MS, since "they are two very distinct diseases." Tr. 93-94; see also Resp. Ex. J at 5-6.

Regarding Dr. Rosenspire's testimony that the Luo et al. narcolepsy paper provided support for molecular mimicry, Dr. Tompkins agreed it was a "great paper" and that the research showed that T cells could be isolated from those who have narcolepsy; however, Dr. Tompkins disagreed that it was relevant in the context of MS. Tr. 106-10 (citing Pet. Ex. 125). In

[47] Mauricio F. Farez et al., Practice Guideline Update Summary: Vaccine-Preventable Infections and Immunization in Multiple Sclerosis, 93 Neurology 584 (2019).

[48] Mauricio F. Farez et al., H1N1 Vaccination Does Not Increase Risk of Relapse in Multiple Sclerosis: A Self-Controlled Case-Series Study, 18 Multiple Sclerosis J. 254 (2012).

[49] For a more detailed discussion of Dr. Tompkins' opinions about why molecular mimicry does not explain how the flu vaccine could cause or exacerbate MS, see Resp. Ex. J at 7-10.

[50] In the transcript, this abbreviation was "CMS," which appears to be an error. See Tr. 91. In the context of the sentence, the abbreviation was probably "CNS," central nervous system.

narcolepsy, "they are looking at HCRT, an antigen that . . . has not been associated with [MS] . . . [as a] target antigen." Tr. 110; see also Resp. Ex. M at 1-2; Resp. Ex. M, Tab 3 at 2.[51]

Dr. Tompkins discussed Libbey et al., an article cited by Petitioner in support of molecular mimicry. Tr. 94-98 (citing Pet. Ex. 28). Libbey et al. discussed different mechanisms relative to MS, and identified molecular mimics, including viral mimics, through research. Tr. 94-96. The authors concluded that research has shown that "molecular mimicry alone cannot result in high enough numbers or activation of CNS-specific autoimmune cells for induction of CNS disease." Pet. Ex. 28 at 15. This observation supports Dr. Tompkins' opinion that there must be more than just a mimic to explain the pathogenesis of MS. See Tr. 97-98; see also Resp. Ex. F, Tab 5 at 9 ("New insights . . . have ruled out the possibility of simple causative associations between genes or the environment and MS.");[52] Resp. Ex. J, Tab 1 (explaining "EBV, sunshine (UVB), smoking and vitamin D, combined with an individual's genetic background, play important roles in the causal pathway that results in MS development," and "[m]igration studies consistently support MS being secondary to an environmental exposure").[53]

On cross-examination, Dr. Tompkins agreed that epidemiological studies regarding vaccines are not universally applicable. Tr. 112. He also conceded that the studies do not show an absence of risk from vaccines; "nothing is safe for everybody all of the time, but the preponderance of data shows that [flu] vaccines are safe for mass use for populations." Tr. 112, 119. He agreed that he was not an epidemiologist. Tr. 118-19. Further, he acknowledged that "molecular mimicry" is a well-accepted "hypothesis," and that it could possibly explain the mechanism and cause and effect of a vaccine injury. Tr. 113. However, he did not believe that molecular mimicry was a likely theory to explain how the flu vaccine can cause MS. Tr. 120.

Regarding Dr. Samuels' reference to bystander activation as a mechanism by which the flu vaccine could cause MS, Dr. Tompkins noted that other than referencing bystander activation, Dr. Samuels failed to explain how the vaccine "would cause bystander activation." Resp. Ex. N at 1-2.

Dr. Tompkins also reviewed both the 2004 IOM report and 2012 IOM report[54] and noted that both reports concluded that the "evidence [was] inadequate to accept or reject a causal relationship" between the flu vaccine and MS. Resp. Ex. N at 2-3 (citing Pet. Ex. 128 at 33; Resp. Ex. A, Tab 2 at 7).

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[51] Daniela Latorre et al., T Cells in Patients with Narcolepsy Target Self-Antigens of Hypocretin Neurons, 562 Nature 63 (2018).

[52] Nils Koch-Henriksen & Per Soelberg Sørensen, The Changing Demographic Pattern of Multiple Sclerosis Epidemiology, 9 Lancet Neurology 520 (2010).

[53] R. Dobson & G. Giovannoni, Multiple Sclerosis – A Review, 26 Eur. J. Neurology 27 (2019).

[54] Inst. of Med., Adverse Effects of Vaccines: Evidence and Causality (Kathleen Stratton et al. eds., 2012).

The more recently reported discovery that EBV infection (mononucleosis infection) may be a risk factor for the development of MS was discussed by Dr. Tompkins. Tr. 96-99, 102-04; see also Resp. Exs. P-Q. He explained that when EBV "infects B cells . . . it transforms [them] to . . . immortal B cell[s]," when then "can be activated independent of any antigen specificity, . . . provid[ing] a way for [] B cells to break tolerance." Tr. 103. He suggested that one proposed mechanism relevant to the pathogenesis of MS is that "B cells that are infected with EBV might be autoreactive against a CNS antigen . . . that triggers the autoimmune response independent of any mimicry." Tr. 103-04. In his final expert report, Dr. Tompkins provided a detailed summary of two 2022 publications that discussed the association between EBV and MS. Resp. Ex. R at 1-3 (citing Resp. Exs. P-Q). Dr. Tompkins concluded that "while knowledge gaps remain, the[se] publications . . . provide compelling evidence and the best evidence to date that a latent/recrudescing [] infection (i.e., EBV) can cause MS by a mechanism of molecular mimicry" and "there is no comparable evidence of causality with a mechanism for a vaccine eliciting autoimmune disease." Id. at 3.

ii. Althen Prongs Two and Three

Instead of vaccination, Dr. Tompkins testified that Petitioner's "[URI] [was] more likely to have caused [] MS than the [flu] vaccination." Tr. 86; see also Resp. Ex. J, at 4, 11; Resp. Ex. N at 3. The basis for his opinion comes from the "epidemiological data around the association from infection to onset of an autoimmune disease, and in this case with [MS]." Tr. 86. For example, De Keyser et al. found that flu-like illnesses/infections were associated with MS flares.[55] Resp. Ex. F, Tab 15 at 1; see also Tr. 86-87. During flu season, these infections include respiratory syncytial virus ("RSV"), adenoviruses, and coronaviruses. Tr. 87. Additionally, adenoviruses, chlamydial infections, and EBV infections have been associated with the onset of MS. Id. On cross-examination, Dr. Tompkins testified that Petitioner's MS symptoms began after his URI but conceded that no specific infectious pathogen related to Petitioner's URI was identified. Tr. 114-16.

Dr. Tompkins disagreed with Dr. Rosenspire's opinion that Petitioner's haplotype provided a basis to reject epidemiology study findings or to argue that his MS was caused by vaccination. See Tr. 50-51, 60-61, 82; Pet. Ex. 120 at 6. Dr. Rosenspire asserted that MS studies were done on Caucasian populations with very different HLA haplotypes, and he argued that the epidemiology studies were therefore not relevant to Petitioner. See Tr. 50-51, 60-61.

Respondent filed two articles showing that the incidence of MS is higher in Black non-Hispanics, especially in women, as compared to their white counter parts. Resp. Ex. L, Tab 2;[56]

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[55] For additional references related to infections and MS, see Pet. Ex. 126; Resp. Ex. L Tab 7 (What Causes MS?, Nat'l Multiple Sclerosis Soc'y, https://www.nationalmssociety.org/What-is-MS/What-Causes-MS (last visited June 28, 2020)).

[56] Eric C. Deussing et al., Estimated Incidence of Multiple Sclerosis Among United Stated Armed Forces Personnel Using the Defense Medical Surveillance System, 177 Military Med. 594 (2012).

Resp. Ex. L, Tab 6.[57] However, in the Langer-Gould et al. article, the authors opined it was "unlikely" there was "genetic risk factor[] unique to blacks" to explain the increased risk "because the prevalence of the main MS susceptibility allele, HLA-DRB1, is lower in blacks than whites and non-HLA risk alleles account for only a small proportion of MS risk in blacks and whites." Resp. Ex. L, Tab 6 at 4 (emphasis omitted). Moreover, the authors noted that the HLA argument "would not explain why the higher risk among blacks is only found in females." Id.

Regarding prong three, Dr. Tompkins agreed that Petitioner's symptoms of MS began following vaccination. Tr. 118.

4. Respondent's Expert, Dr. David N. Alexander, M.D.[58]

a. Background and Qualifications

After receiving his M.D. from the University of Minnesota, Dr. Alexander completed an internal medicine internship at University Hospital, Boston University Medical Center and a neurology residency at Neurological Institute of New York, Columbia Presbyterian Medical Center. Resp. Ex. B at 1; Tr. 171. Thereafter, he began working and teaching at the University of California, Los Angeles ("UCLA"). Resp. Ex. B at 1-2; Tr. 171-72. He saw patients for over 40 years, including patients with MS. Tr. 172-73. Dr. Alexander also sat on the board for UCLA's Marilyn Hilton MS Achievement Center for 14 years. Tr. 173. He taught medical students, neurology residents, and fellows over the course of his 40 years at UCLA. Tr. 173-74. In July 2022, Dr. Alexander retired. Tr. 171-172.

b. Opinion

i. Althen Prong One

Dr. Alexander opined that the flu vaccine has not been shown to cause MS. Tr. 175. He opined that "MS is a disease of unknown cause." Resp. Ex. A at 4. In support of his opinion that there is no evidence that the flu vaccine can cause MS, Dr. Alexander cited Farez and Correale (2011).[59] Resp. Ex. A, Tab 1. The authors conducted a systematic review of publications from 1966 to 2011 and found "[n]o significant change in the risk of developing MS after vaccination for . . . [flu]." Id. at 1. Further, the flu vaccination was not associated with a risk of MS relapse. Id. More recent articles have concluded "[s]tandard immunization protocols

[57] Annette Langer-Gould et al., Incidence of Multiple Sclerosis in Multiple Racial and Ethnic Groups, 80 Neurology 1734 (2013).

[58] Dr. Alexander submitted three expert reports and testified at the hearing. Resp. Exs. A, E, O; Tr. 169.

[59] Mauricio F. Farez & Jorge Correale, Immunizations and Risk of Multiple Sclerosis: A Systematic Review and Meta-Analysis, 258 J. Neurology 1197 (2011).

are not contributing towards greater MS risk and higher disease activity." Resp. Ex. L, Tab 5 at 16.[60]

Dr. Alexander cited some of the same studies referenced by Dr. Tompkins, including the systematic literature review authored by Mailand and Frederiksen. See Resp. Ex. H, Tab 2. "The study found no change in risk of developing [MS] after vaccination," including after the seasonal flu vaccine. Id. at 1. Next, Dr. Alexander discussed the Bavarian study by Hapfelmeier et al. and editorial paper by Yeh and Graves.[61] See Resp. Ex. H, Tabs 10-11. Yeh and Graves noted that the Hapfelmeier et al. did not find any association between vaccinations and MS. Resp. Ex. H Tab 11 at 1-2 (citing Resp. Ex. H, Tab 10). Further, Yeh and Graves reported that Hapfelmeier et al. supported a finding "that there may be a protective effect of vaccines in MS." Id. at 2.

After discussing the lack of association between vaccination and MS, Dr. Alexander also explained that infections do not cause flares of symptoms of MS. Tr. 178. He opined that infections could make those with MS ill and lead to "a functional decline," but infections do not cause the formation of new MS plaques. Id. In other words, an infection can "exacerbate[] a pre-existing deficit and make[] it worse," but this functional decline is temporary. Tr. 178-79.

Regarding the mechanism of molecular mimicry, Dr. Alexander opined that it was "often invoked" in the context of vaccines and autoimmune diseases, but that it is "not particularly applicable in this case." Tr. 179-80. He further testified that molecular mimicry is "not specific" to MS. Tr. 180.

Dr. Alexander expressed concern about how Dr. Samuels cited the 2004 IOM report but failed to include important aspects of this report. Resp. Ex. O at 1-3. First, he noted Dr. Samuels failed to quote the conclusion "that there [was] weak evidence for biological mechanisms related to . . . molecular mimicry and bystander activation, by which receipt of any [flu] vaccine could possibly influence an individual's risk of developing . . . MS." Id. at 2 (quoting Pet. Ex. 128 at 29). He also noted that the same conclusion, specifically that there was "a lack of association between [the] [flu] vaccine and the onset of MS in adults," was reached in the 2012 IOM report. Id. at 3 (citing Resp. Ex. A, Tab 2 at 7).

In response to Dr. Rosenspire's use of GBS to support his opinions about molecular mimicry in the context of MS, Dr. Alexander raised several concerns. Resp. Ex. E at 1-2. Dr. Alexander opined that GBS and MS are "very different diseases, and neither target[] 'nerves' or neurons." Id. at 1. Dr. Alexander explained that MS is "characterized by the production of anti-bodies within the immunologically protected CNS, whereas GBS does not have a CNS component, and the immunologic response is generated entirely by structures outside the brain." Id. at 2. More specifically, GBS involves "an attack in the peripheral nervous system on Schwann cells, and MS is an attack in the [CNS] on oligodendrocytes, two different cell types"

[60] Dejan Jakimovski et al., Infections, Vaccines and Autoimmunity: A Multiple Sclerosis Perspective, 8 Vaccines 1 (2020).

[61] E. Ann Yeh & Jennifer Graves, Vaccination: Not a Trigger for MS, 93 Neurology 377 (2019).

that differ in "development, morphology, associated diseases, and biochemically." Id. at 1. Moreover, they arise from different origins and are embryologically distinct.[62] Id. Further, GBS is "an acute monophasic illness, reaching a nadir by [three] weeks and gradually recovering after that," while MS "is a relapsing and remitting and chronic disorder, with a variable onset and no prospectively definable nadir." Id. at 2.

ii. Althen Prongs Two and Three

Dr. Alexander opined that the flu vaccine Petitioner received on October 4, 2011 did not cause or significantly aggravate his MS, and the vaccine has not been shown to either cause or aggravate the illness. Tr. 175.

Regarding Petitioner's clinical course, Dr. Alexander specifically disagreed with Dr. Samuels' opinion that Petitioner had an aggressive onset of MS. Tr. 191-92. To rebut this opinion, Dr. Alexander reviewed Petitioner's MRI reports and compared the reports from 2011 to those done in 2012. He opined that "[t]he MRIs show multiple patchy areas of both old and new lesions that change over time" and "[t]he spinal cord involvement is [] incomplete." Tr. 191. Overall, he concluded that these studies do not show "an aggressive form of MS." Id. In contrast, he opined aggressive forms of MS are usually seen in young patients, ages 20 to 30, who are non-ambulatory within one to two years. Id. By comparison, based on Petitioner's clinical course and MRI reports, Dr. Alexander opined that Petitioner's course was within the range of usual MS. Tr. 192-93. Moreover, Dr. Alexander opined that there is no known difference in the pathology of early-onset versus late-onset MS. Tr. 193.

Based on his review of Petitioner's brain MRI reports in 2011 and 2012, Dr. Alexander opined that the brain lesions described in 2011 are not sufficiently described to allow him to conclude that they are MS lesions, since they could also be consistent with small vessel disease. Tr. 198-99. He noted, however, that the brain MRI report in 2012 identified "Dawson's fingers,"[63] a very typical MS finding. Tr. 182. In 2012, the lesions were not enhanced, indicating the lesions were not new, but old and not active. Tr. 182-83. Since the lesions were old, Dr. Alexander suspected they were present on the 2011 scan, and even before then, because the 2011 report does not describe enhancement of the lesions. Tr. 183-84, 199. However, Dr. Alexander could not say, more likely than not, the white matter lesions were the same in 2011 and 2012, or that they predated 2011. Tr. 199-200. Although he suspected the brain lesions were present before vaccination, he does not hold that opinion to the "more likely than not" standard. Tr. 183, 199-201. He opined that without prior MRI studies, one is unable to date the onset of Petitioner's MS. Tr. 201-02. In conclusion, because Petitioner had no history of symptoms prior to vaccination, and there are no older baseline MRI studies to compare with the

[62] For a description of Schwann cells and oligodendrocytes, see Resp. Ex. E, Tab 2 (Principles of Neural Science (Eric R. Kandel eds., 4th ed. 2000)). Only two non-consecutive pages of this book were filed.

[63] Dr. Alexander testified that Dawson's fingers are "little white matter tracts that emanate from the corpus callosum, and signal intensity there, plaques there, [] characteristic of [MS]." Tr. 182.

post-vaccination MRI studies, Dr. Alexander did not opine that Petitioner's MS predated his vaccination. Tr. 203.

Dr. Alexander also noted Petitioner had abnormalities of his cervical and thoracic spine reported on his MRIs done in both 2011 and 2012. Tr. 186-90. Dr. Alexander testified that there were multiple plaques, described in 2011 as "patchy enhancement" in several areas of the cervical cord at C2, then at C6/7 to T1, and down to T5. Tr. 186-87. In 2011, the lesions were described as enhanced, which indicates they were relatively new. Tr. 187. The 2012 cervical and thoracic MRI done four to five months later again showed active disease with enhancing lesions in the spinal cord. Tr. 188. Dr. Alexander also opined that these reports confirmed the diagnosis of MS. Tr. 188, 190.

While Dr. Alexander agreed that Petitioner's age at MS onset "[was] uncommon, but not rare," he did not agree that this fact weighed in favor of vaccine causation. Resp. Ex. E at 2-3. Dr. Alexander opined that "[d]espite a later age of onset, there is nothing that indicates a different pathophysiology or cause." Id. at 2. In support of this opinion, Dr. Alexander cited the Polliack et al. paper on late-onset MS. Id. (citing Pet. Ex. 21). "Late-onset MS was defined as the first presentation of clinical symptoms after the age of 50 years." Pet. Ex. 21 at 2. The authors found that the presentation of depression in older patients may herald the possibility of MS. Id. at 4. They did not describe any differences in pathogenesis or pathophysiology of late-onset disease as compared to early-onset patients. See id.

IV. DISCUSSION

A. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Hum. Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, Petitioner may satisfy his burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

In particular, Petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321

(quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. A petitioner who satisfies this burden is entitled to compensation unless Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

"Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case." Flores v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 157, 162-63 (2014); see also Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations.").

B. Causation

To receive compensation through the Program, Petitioner must prove either (1) that he suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that he suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Petitioner must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because Petitioner does not allege he suffered a Table Injury, he must prove a vaccine he received caused his injury. To do so, Petitioner must establish, by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. Petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d. 543, 548-49 (Fed. Cir. 1994). Petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether a petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is

contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in Petitioner's favor when the evidence weighs in his favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioner's favor).

Testimony that merely expresses the possibility—not the probability—is insufficient, by itself, to substantiate a claim that such an injury occurred. See Waterman v. Sec'y of Health & Hum. Servs., 123 Fed. Cl. 564, 573-74 (2015) (denying Petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard). The Federal Circuit has made clear that the mere possibility of a link between a vaccination and a petitioner's injury is not sufficient to satisfy the preponderance standard. Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence); Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019). While certainty is by no means required, a possible mechanism does not rise to the level of preponderance. Moberly, 592 F.3d at 1322; see also de Bazan, 539 F.3d at 1351.

V. CAUSATION ANALYSIS

A. Althen Prong One

Under Althen prong one, Petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu, 569 F.3d at 1375; Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. Boatmon, 941 F.3d at 1359; see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioner relies upon a medical opinion to support his theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The undersigned finds Petitioner failed to provide preponderant evidence of a sound and reliable theory to explain how the flu vaccine can cause MS. There are several reasons for this finding.

First, the undersigned acknowledges that Petitioner need not make a specific type of evidentiary showing or require identification of a specific antigenic trigger for an immune-

mediated pathology to prove that a theory is sound and reliable by preponderant evidence. Given the state of current scientific knowledge, there is no way that a petitioner could satisfy such a requirement, especially here, where Dr. Rosenspire conceded that a specific antigen is not known.[64] Further, requiring proof of the identify of a specific antigen to prove causation would require scientific certainty, which is a bar too high. See Knudsen, 35 F.3d at 549 (explaining that "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program").

However, based on the current understanding of the etiology of MS described in the literature filed herein, Petitioner's proposed mechanisms of molecular mimicry and bystander activation fall short because there is no medical literature or any other evidence to show that more likely than not, the flu vaccine can cause MS or that it causes MS via molecular mimicry and/or bystander activation. Petitioner's immunology expert, Dr. Rosenspire, acknowledged that the cause of MS is unknown. See Pet. Ex. 105 at 3. He testified that there is uncertainty about what triggers the cause of the illness. See Tr. 32-33. And ultimately, Dr. Rosenspire referenced the causal mechanism as the "whatever mechanism, be it molecular mimicry, or the so far undefined mechanism(s)." Pet. Ex. 107 at 2.

The literature filed by the parties is replete with statements that the cause of MS is not known. See, e.g., Pet. Ex. 28 at 2 ("The etiology of MS is unknown."); Resp. Ex. L, Tab 7 at 1 ("The cause of MS is not known."). Current medical literature rejects the simplistic notion that a one-time occurrence of immune activation due to vaccination can cause MS, even if molecular mimicry may play a role in one step of disease pathogenesis. In 2006, Sospedra and Martin wrote, "it has become clear that molecular similarities between foreign and self proteins are usually not sufficient to lead to pathological consequences." Resp. Ex. F, Tab 28 at 2. Kanduc et al. wrote in 2008 that "the massive viral to human peptide overlapping calls into question the possibility of a direct causal association between virus-host sharing of amino acid sequences and incitement to autoimmune reactions through molecular recognition of common motifs." Resp. Ex. F, Tab 31 at 1. And in 2010, Koch-Henriksen and Sørensen stated that "[n]ew insights . . . have ruled out the possibility of simple causative associations between genes or the environment and MS." Resp. Ex. F, Tab 5 at 9.

In contrast to earlier papers that Petitioner's expert cited that discuss molecular mimicry, Dobson and Giovannoni, a 2019 article cited by Dr. Tompkins, provides a more current summary of what is known about the underlying cause of MS. Resp. Ex. J, Tab 1. While the authors maintained that "the cause [of MS] remains uncertain," they added that "MS is a complex disease; many genes modestly increase disease susceptibility in addition to several well defined environmental facts, in particular vitamin D or ultraviolet B light (UVB) exposure, [EBV] infection, obesity[,] and smoking." Id. at 1.

Although molecular mimicry is an accepted scientific mechanism, generally opining that molecular mimicry is a causal theory, without more, is insufficient. See, e.g., W.C. v. Sec'y of Health & Hum. Servs., 704 F.3d 1352, 1360 (Fed. Cir. 2013) (noting "[t]he special master found

[64] See Tr. 63 (testifying that the cross-reactive epitopes in the flu vaccine which cause MS are not known).

that molecular mimicry is a well-regarded theory in some contexts, but correctly required additional evidence showing that molecular mimicry can cause the [flu] vaccine to significantly aggravate [MS]" (internal citations and quotations omitted) (citing Broekelschen, 618 F.3d at 1345)); Loyd ex rel. v. Sec'y of Health & Hum. Servs., No. 16-811V, 2021 WL 2708941, at *31 (Fed. Cl. Spec. Mstr. May 20, 2021) ("[T]hough molecular mimicry is a generally accepted scientific concept, and is frequently invoked in Program cases, the mere mention of it does not constitute satisfaction of the preponderant evidentiary standard. Rather, it must be shown that the mechanism likely does link the vaccine in question to the relevant injury." (internal citations omitted)); McKown v. Sec'y of Health & Hum. Servs., No. 15-1451V, 2019 WL 4072113, at *50 (Fed. Cl. Spec. Mstr. July 15, 2019) (explaining that "merely chanting the magic words 'molecular mimicry' in a Vaccine Act case does not render a causation theory scientifically reliable, absent additional evidence specifically tying the mechanism to the injury and/or vaccine in question" (emphasis omitted)); Johnson v. Sec'y of Health & Hum. Servs., No. 14-254V, 2018 WL 2051760, at *26 (Fed. Cl. Spec. Mstr. Mar. 23, 2018) ("Petitioners cannot simply invoke the concept of molecular mimicry and call it a day. Rather, they need to offer reliable and persuasive medical or scientific evidence of some kind (whether expert testimony or literature) . . . . (internal citations omitted) (emphasis omitted)); Mattus-Long v. Sec'y of Health & Hum. Servs., No. 15-113V, 2022 WL 4242140, at *27 (Fed. Cl. Spec. Mstr. Aug. 31, 2022) (noting "the mere mention of molecular mimicry is not a 'get out of jail free card' in the Program, entitling claimants to compensation, merely because it has scientific reliability as a general matter"); Sheets v. Sec'y of Health & Hum. Servs., No. 16-1173V, 2019 WL 2296212, at *17 (Fed. Cl. Spec. Mstr. Apr. 30, 2019) (determining Petitioner had not satisfied Althen prong one when he did not relate molecular mimicry "to either the vaccines in question or Petitioner's own specific condition").

Moreover, Respondent filed numerous and more recent studies that examined whether the flu vaccine increases the risk of MS or the risk of MS relapse, and these studies also do not show a causal association.[65] For example, Farez and Correale (2011) performed a systematic medical literature search from 1966 to 2011, and found no increased risk of developing MS or a relapse of MS. Resp. Ex. A, Tab 1 at 1, 7-8. Bardage et al. (2011) reported on a Swedish study that found no increased risk of MS in those vaccinated with flu. Resp. Ex. F, Tab 9 at 1. Other studies, including some that are older, came to the same conclusions. See, e.g., Resp. Ex. F, Tab 16 at 1 ("[Flu] immunization in MS patients is neither associated with an increased exacerbation rate in the postvaccination period nor a change in disease course over the subsequent 6 months."); Resp. Ex. F, Tab 15 at 1-2; Resp. Ex. F, Tab 13 at 1; Resp. Ex. F, Tab 17 at 1 ("No patient reported any new neurological symptoms following the use of either [the seasonal flu or H1N1v flu] vaccine."); Resp. Ex. J, Tab 6 at 2-3.

A 2016 article stated, "there has been no substantiation to reports suggesting a link between vaccination and the development of MS." Resp. Ex. J, Tab 6 at 2. Mailand and Frederiksen (2017) "found no change in risk of developing [MS] after vaccination against . . .

[65] The undersigned acknowledges that "[s]everal early case reports [] suggested that relapse or onset of MS [could] follow vaccination against [flu]." Resp. Ex. F, Tab 12 at 3. However, "carefully controlled studies have not demonstrated an increase in relapse rate or progression of disability following [flu] vaccination." Id.

seasonal [flu]." Resp. Ex. H, Tab 2 at 1. Hepfelmeier et al., in 2019, similarly found their study "[did] not reveal vaccination to be a risk factor for MS," and, in fact, their results "suggest[ed] that vaccination is associated with a lower likelihood of being diagnosed with MS." Resp. Ex. H, Tab 10 at 1; see also Resp. Ex. J, Tab 9 at 1 (indicating, in 2019, that "[c]linicians should recommend that patients with MS receive the [flu] vaccination annually"); Resp. Ex. L, Tab 5 at 1 (finding "[t]here is currently no sufficient evidence to support associations between standard vaccine policies and an increased risk of MS" in 2020).

Although a petitioner need not make a specific type of evidential showing (i.e., epidemiologic studies) to satisfy his burden, special masters shall still consider and weigh the evidence in the record, including the epidemiological studies filed. See § 13(b)(1) (indicating the special master shall consider all materials in the record); Capizzano, 440 F.3d at 1325-26; Grant v. Sec'y of Health & Hum. Servs., 956 F.2d 1144, 1149 (Fed. Cir. 1992) (finding "epidemiological studies are probative medical evidence relevant to causation" and "considerable weight [is] due to epidemiological studies in the absence of direct evidence of actual causation"). And after weighing the submitted evidence, the undersigned finds the evidence does not weigh in Petitioner's favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."). The undersigned finds the totality of the evidence presented demonstrates no link between the flu vaccine and the development of MS.

Further, the undersigned does not find Petitioner's examples based on GBS and narcolepsy to be persuasive evidence that the flu vaccine can cause MS even assuming that molecular mimicry is the causal mechanism for GBS and narcolepsy. As explained by Respondent's experts, these two diseases are different than MS. There is evidence that the host antigens differ between GBS and MS. See, e.g., Pet. Ex. 35 at 3 tbl.1. And Latorre et al., for example, does not support molecular mimicry between flu antigen and HCRT, which is the host target in narcolepsy. Resp. Ex. M, Tab 3 at 2.

More recently there has been a focus on the causal role of EBV infection in MS. Two 2022 articles filed by Respondent[66] suggest that EBV infection may be a potential cause of MS based on new research and studies. One article, Lanz et al., suggested that molecular mimicry may potentially play a role in EBV causation of MS. Whether future studies will replicate the

[66] The first article, Bjornevik et al., reported on a study of MS cases in a group of active-duty US military personnel between 1993 and 2013, using serum samples to determine EBV status. Resp. Ex. P at 1. They documented 955 MS cases, and studied serum samples collected before the date of onset in 801 of the cases. Id. Only one of 801 cases of MS occurred in a person who was EBV negative in a sample prior to disease onset. Id. The study showed that EBV infection preceded MS onset and was associated with higher disease risk. Id. at 3. "Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other virus . . . ." Id. at 1. The authors concluded that EBV may be "the leading cause of MS." Id. The second study, by Lanz et al, showed evidence of molecular mimicry between an "EBV nuclear antigen 1 [] and the [CNS] protein glial cell adhesion molecule." Resp. Ex. Q at 1. The authors concluded that their "results provide a mechanistic link for the association between MS and EBV." Id.

finding that EBV infection and/or molecular mimicry play a causal role in MS remains to be seen. What is clear, however, is that the evidence filed in this case does not establish that the flu vaccine can cause MS.

Finally, there are other Program cases with reasoned analyses regarding whether the flu vaccination can cause or aggravate MS via molecular mimicry, where the special masters denied entitlement. One of these cases was appealed to the Federal Circuit, who affirmed the judgment of the Court of Federal Claims upholding the special master's decision denying compensation. See W.C., 704 F.3d 1352. In W.C., Petitioner alleged that a flu vaccine caused or significantly aggravated MS via the mechanism of molecular mimicry.[67] Id. at 1354-55. Then Chief Judge Rader found that the special master "correctly required additional evidence showing that molecular mimicry can cause the [flu] vaccine to significantly aggravate [MS]." Id. at 1360. Moreover, Petitioner "did not provide evidence that any peptide from the [flu] vaccine he received was cross-reactive with myelin basic protein-specific T cells" thought to trigger the cross-reactive immune response. Id. Thus, the Federal Circuit held that the special master's finding as to the lack of evidence of a supportive medical theory was not arbitrary or capricious. Id. at 1361.

Since Chief Judge Radar's holding in W.C. in 2013, there have been no other Federal Circuit opinions addressing the mechanism of molecular mimicry in the context of a flu vaccine and MS. There have been cases decided by special masters on the issue of whether a flu vaccination can significantly aggravate MS where molecular mimicry was posited as the causal theory; however, these cases involved different facts and evidence.[68] Further, rulings and decisions by other special masters are not binding on the undersigned. See Boatmon, 941 F.3d at 1358; Hanlon v. Sec'y of Health & Hum. Servs., 40 Fed. Cl. 625, 630 (1998), aff'd, 191 F.3d 1344 (Fed. Cir. 1999).

Overall, the undersigned finds that here, Petitioner's theories are unsupported by medical or scientific facts, research, or any other reliable evidence. As such, the theories are speculative and/or conclusory in nature. When evaluating whether petitioners have carried their burden of proof, special masters consistently reject "conclusory expert statements that are not themselves backed up with reliable scientific support." Kreizenbeck v. Sec'y of Health & Hum. Servs., No. 08-209V, 2018 WL 3679843, at *31 (Fed. Cl. Spec. Mstr. June 22, 2018), mot. for rev. denied, decision aff'd, 141 Fed. Cl. 138, aff'd, 945 F.3d 1362 (Fed. Cir. 2020). The undersigned will not rely on "opinion evidence that is connected to existing data only by the ipse dixit of the expert." Prokopeas v. Sec'y of Health & Hum. Servs., No. 04-1717V, 2019 WL 2509626, at *19 (Fed. Cl. Spec. Mstr. May 24, 2019) (quoting Moberly, 592 F.3d at 1315). Instead, special masters are expected to scrutinize the reliability of each expert report submitted. See id.

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[67] In W.C., the special master also found that the onset of Petitioner's MS preceded vaccination, and thus could not have caused it. W.C., 704 F.3d at 1356.

[68] See, e.g., Robinson v. Sec'y of Health & Hum. Servs., No. 14-952V, 2021 WL 2371721 (Fed. Cl. Spec. Mstr. Apr. 12, 2021); P.M. v. Sec'y of Health & Hum. Servs., No. 16-949V, 2019 WL 5608859 (Fed. Cl. Spec. Mstr. Oct. 31, 2019); Quackenbush-Baker v. Sec'y of Health & Hum. Servs., No. 14-1000V, 2018 WL 1704523 (Fed. Cl. Spec. Mstr. Mar. 14, 2018).

In summary, Petitioner has failed to offer a sound and reliable medical theory in support of his claim. Thus, the undersigned finds Petitioner has failed to provide preponderant evidence with respect to the first Althen prong.

B. Althen Prong Two

Under Althen prong two, Petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. Andreu, 569 F.3d at 1367; Capizzano, 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" (quoting Althen, 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. Cucuras, 993 F.2d at 1528. Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano, 440 F.3d at 1325. Instead, Petitioner may satisfy his burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

Since Petitioner failed to prove Althen prong one, it follows that he cannot prove Althen prong two. However, even if Petitioner had proven Althen prong one, the undersigned finds Petitioner has failed to show by preponderant evidence that there is a logical sequence of cause and effect showing Petitioner's flu vaccine caused his MS.

Petitioner's expert, Dr. Rosenspire, offered three reasons why it was more likely than not that the flu vaccine was a substantial contributing cause for Petitioner's MS. The first was because the flu vaccination preceded the onset of his illness, which is discussed in more detail below. The second reason was because Petitioner had late-onset MS, which suggested to Dr. Rosenspire that the vaccine was causally related. The medical literature filed by the parties related to late-onset MS, however, does not support Dr. Rosenspire's premise. None of the articles suggest that the pathogenesis of late-onset MS differs from early-onset MS, or that late-onset MS is likely to be vaccine-related. And at the hearing, Dr. Rosenspire conceded that there is no known specific difference between the cause of MS in late-onset patients as compared to younger patients. Tr. 59.

Late-onset MS is the subject matter of several articles filed by the parties.[69] These articles describe the clinical characteristics of late-onset MS but none of them suggest that the

[69] See, e.g., Pet. Exs. 20-23.

cause of late-onset MS differs from that of earlier onset MS. And none of the articles provide any evidence upon which one could conclude that late-onset MS is likely to be caused by vaccination. The Langer-Gould et al. case-control study, which used data from Kaiser Permanente South California patients from 2008 to 2011, reported that "vaccination of any type was associated with an increased risk of CNS [acquired demyelinating syndromes, including MS] within the first 30 days after vaccination only in younger (< 50 years) individuals." Resp. Ex. F, Tab 8 at 1. The authors reported "no association between any vaccination and CNS [acquired demyelinating syndromes] in older individuals during any time interval." Id. at 4. Further, there was "no long[]-term association of vaccines with MS," which they concluded "argues against a causal association." Id. at 1, 7. As for the short-term increased risk in younger patients, the authors posited that "vaccines may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease." Id. Otherwise, the authors did not propose any difference in pathogenesis between early- and late-onset MS based on their findings. As it relates to the present case, the Langer-Gould et al. study findings argue against a causal association in late-onset MS generally, and especially here, since Petitioner was 57 years old at onset of his MS symptoms.

The third reason Dr. Rosenspire opined that Petitioner's MS was vaccine-related was based on Petitioner's haplotype. He asserted that the MS studies done on Caucasian populations represent a very different HLA haplotype, and thus, the epidemiology studies are irrelevant as to Petitioner. But Dr. Rosenspire's opinion that Petitioner's haplotype contributed to his MS was based on his "guess." Tr. 60-61. Thus, his opinion is speculative, and does not meet the preponderance standard. See Waterman, 123 Fed. Cl. at 573-74 (noting that a possible causal link was not sufficient to meet the preponderance standard); Moberly, 592 F.3d at 1322; Kreizenbeck, 2018 WL 3679843, at *31 (explaining special masters consistently reject "conclusory expert statements that are not themselves backed up with reliable scientific support"), mot. for rev. denied, decision aff'd, 141 Fed. Cl. 138 (2018), aff'd, 945 F.3d 1362 (Fed. Cir. 2020). The undersigned will not rely on "opinion evidence that is connected to existing data only by the ipse dixit of the expert;" instead, the undersigned must carefully scrutinize the reliability of each expert report submitted. Prokopeas, 2019 WL 2509626, at *19 (quoting Moberly, 592 F.3d at 1315).

Further, Dr. Rosenspire's opinion is not supported by the medical literature. Langer-Gould et al. stated it was "unlikely" there was "genetic risk factor[] unique to blacks" to explain the increased risk "because the prevalence of the main MS susceptibility allele, HLA-DRB1, is lower in blacks than whites and non-HLA risk alleles account for only a small proportion of MS risk in blacks and whites." Resp. Ex. L, Tab 6 at 4 (emphasis omitted). Moreover, the HLA argument "would not explain why the higher risk among blacks is only found in females." Id. Thus, Dr. Rosenspire's argument based on HLA haplotype is not supported by the evidence.

Dr. Samuels opined that Petitioner's aggressive clinical course supported vaccine causation. Dr. Alexander specifically disagreed based on Petitioner's MRI reports, which did not show "an aggressive form of MS."[70] Tr. 191. Moreover, Dr. Alexander opined that there is no

[70] The undersigned notes that in 2012, Petitioner's physician referred to his clinical course as "aggressive." Pet. Ex. 6 at 253.

known difference in the pathology of early- versus late-onset MS. Regardless of whether Petitioner's course was aggressive or not, Petitioner did not offer any evidence to show that this fact supported a finding that the cause of his MS was his vaccine.

Next, Petitioner filed a letter authored by his physician, Dr. West, stating his opinion that the flu vaccine "given on October 4, 2011 led to the onset of this [CNS] demyelinating disease" (MS). Pet. Ex. 6 at 350. Dr. West, however, did not explain or describe the basis for his opinion. Case law provides that treating physician statements are typically "favored" as they "are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" Capizzano, 440 F.3d at 1326 (quoting Althen, 418 F.3d at 1280). A treating physician's views, however, do not bind the special master, per se; rather, their views are to be carefully considered and evaluated. § 13(b)(1); Snyder, 88 Fed. Cl. at 746 n.67. Importantly, "[a]s with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases." Welch v. Sec'y of Health & Hum. Servs., No. 18-494V, 2019 WL 3494360, at *8 (Fed. Cl. Spec. Mstr. July 2, 2019).

While the undersigned has carefully considered Dr. West's opinion, she finds that because he did not provide any foundational basis for his opinion, it does not provide preponderant evidence of causation, especially given the lack of evidence that the flu vaccine can cause MS. Further, the undersigned finds Dr. West's opinion to be conclusory in nature and without support. See Kreizenbeck, 2018 WL 3679843, at *31; Prokopeas, 2019 WL 2509626, at *19.

Lastly, Respondent's expert, Dr. Tompkins, raised the question of whether Petitioner had an URI that led to his development of MS. Petitioner received his flu vaccination on October 4, 2011. The medical records show that on November 2, 2011, Petitioner presented to an urgent care clinic for cough and sore throat for the past two weeks. His chief complaint was "congestion, sinus pressure x 12 days." Pet. Ex. 10 at 471. Assessment was URI. After Petitioner was admitted to Valley Hospital, he reported that he had a cough and cold beginning October 13, 2011. These records support Dr. Tompkins' opinion that Petitioner had an URI prior to the onset of his MS. But testing was not done to identify any specific pathogen. Dr. Tompkins filed medical literature supporting his opinion that URIs have been causally associated with the onset and exacerbations of MS. See Pet. Ex. 126 at 8.

The undersigned acknowledges that Petitioner is not required to eliminate other potential causes in order to be entitled to compensation. See Walther v. Sec'y of Health & Hum. Servs., 485 F.3d 1146, 1149-52 (Fed. Cir. 2007) (finding a petitioner does not bear the burden of eliminating alternative independent potential causes). However, the undersigned finds it reasonable to consider "evidence of other possible sources of injury"—here, Petitioner's URI—in determining "whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question." Stone, 676 F.3d at 1379. Based on the records and opinion of Dr. Tompkins, the undersigned finds there is evidence of another possible cause of MS, Petitioner's URI. This determination, along with the lack of evidence that the flu vaccine

can cause MS, contributes to the weight of evidence against finding that Petitioner has proven a logical sequence of cause and effect.[71]

Accordingly, the undersigned finds that Petitioner has failed to provide preponderant evidence of a logical sequence of cause and effect to satisfy his burden under Althen prong two.

C. Althen Prong Three

Althen prong three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That term has been defined as a "medically acceptable temporal relationship." Id. Petitioner must offer "preponderant proof that the onset of symptoms occurred within a time frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen prong one). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542; see also Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer, 100 Fed. Cl. at 356 (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that [P]etitioner must posit a medical theory causally connecting the vaccine and injury").

The parties stipulated that Petitioner received a flu vaccine on October 4, 2011. In their stipulated facts, the parties agreed that "[a]s of November 2, 2011, Petitioner had a two to three week history of cough and sore throat that was getting worse." Joint Prehearing Submission at 1. On November 14, 2011, Petitioner had "'hand tremors' reported to be of one month duration." Id. And on November 25, 2011, Petitioner presented to the ER for numbness in his arms, neck pain, and difficulty walking, which began about ten days before.

Dr. Rosenspire alternatively opined that Petitioner's symptoms began approximately ten days following his flu vaccination, and that molecular mimicry would result in "an immune response to self epitopes in two to three weeks." Tr. 66; see also Pet. Ex. 107 at 3-4. Dr. Rosenspire did not describe the symptoms which he believes occurred ten days post-vaccination or two to three weeks after vaccination. Dr. Samuels testified that Petitioner received his flu vaccine on October 4, and developed flu like symptoms about ten days later, followed by a loss of balance, numbness, clumsiness, and tremors on November 29, 2011.

Respondent's experts did not refute Petitioner's experts' opinions that there was an appropriate temporal association between vaccination and the onset of Petitioner's MS. Dr. Tompkins agreed that Petitioner's symptoms of MS began following vaccination and Dr. Alexander did not specifically address onset. Thus, Respondent does not dispute that there is a temporal association between Petitioner's flu vaccination and the onset of his MS.

[71] Even without this possible cause (URI), the undersigned finds Petitioner has not provided preponderant evidence of a logical sequence of cause and effect.

For these reasons, the undersigned finds that Petitioner has provided preponderant evidence satisfying Althen prong three. However, a temporal association, without more, is insufficient. Moberly, 592 F.3d at 1323; Grant, 956 F.2d at 1148 ("[A] proximate temporal association alone does not suffice to show a causal link between the vaccination and the injury."). Therefore, Petitioner is not entitled to compensation.

VI. CONCLUSION

The undersigned extends her sympathy to Petitioner for the pain and suffering and disability that he has experienced due to his illness. The undersigned's Decision, however, cannot be decided based upon sympathy, but rather on the evidence and law.

For the reasons discussed above, the undersigned finds that Petitioner has failed to establish by preponderant evidence that his flu vaccination caused his MS. Therefore, Petitioner is not entitled to compensation and the petition must be dismissed. In the absence of a timely filed motion for review pursuant to Vaccine Rule 23, the Clerk of Court **SHALL ENTER JUDGMENT** in accordance with this Decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master